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Standardization of the Ballistocardiogram by Simulation of the Heart's Function at Necropsy; With a Clinical Method for the Estimation of Cardiac Strength and Normal Standards for It

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The interpretation of ballistocardiograms has been attacked by a method entirely new; a physiologic experiment performed at necropsy. While the subject lies on the ballistocardiograph a normal diastolic pressure is created and the heart's function is simulated by injecting fluid into the aorta and pulmonary artery, the amount injected at each instant being recorded. The resulting ballistocardiograms can be directly compared with many aspects of cardiac function. The amplitude of the ballistocardiogram measures the maximum force exerted by the heart in moving the blood and preliminary normal standards for this estimate of cardiac strength have been set up.

THE THEORY of the ballistocardiogram aims to account for the recorded waves by forces generated by the heart, and imparted to the blood. At the first attempts to define this relationship many assumptions were necessary, the chief of which concerned the contour of the cardiac ejection curve. Thus Starr, Rawson, Schroeder and Joseph[1] and Starr and Rawson[2], assumed that this curve for man was similar to a curve measured in an experiment on an anesthetized dog; while Hamilton, Dow and Remington[3] employed a curve which had been calculated from measurements of aortic elasticity made in several dogs and one cadaver soon after death. Though differing in some details, the conclusions drawn from these studies agreed in the essentials; the deflections of the ballistocardiogram were attributed to forces generated by the heart when the blood was moved, and the contour of the tracing was related to the shape of the cardiac ejection curve.

Experiments, interrupted by the war, have now been performed on fresh cadavers in which the cardiac contraction was simulated by injecting fluid into the aorta and pulmonary artery in amounts recorded at each instant of time. By obtaining ballistocardiograms simultaneously, we found ourselves in a position to compare these records with the movement of the "blood," and so to put the theory on much firmer ground. Over one hundred such comparisons have been made. The results show that the contour of the ballistocardiogram is mathematically related to the cardiac ejection curve; this presentation will stress this aspect of our results.

In addition, these experiments have permitted us to test our old conceptions of the genesis of ballistocardiograms,[1, 2] confirming many and disproving some of them; most important, the new techniques have provided a method of testing the accuracy of any esti-

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mate of cardiac function we may set up. Thus we explored a new approach to the estimation of cardiac output and found that the proposed method was too inaccurate. Nevertheless, from this line of thought came a method of estimating the contour of the cardiac ejection curve from the ballistocardiogram. Finally a simple method was devised for estimating the maximal force developed in any systole, in relative terms, from the ballistocardiogram. This method proved to have an accuracy equal to that of the auscultatory estimate of systolic pressure, so normal standards were set up for it.

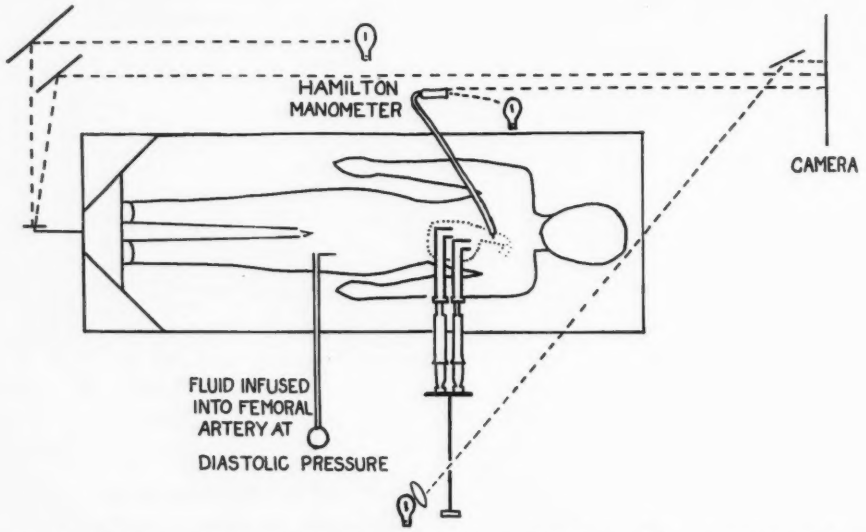

FIG. 1.—Arrangement of Apparatus. For description see text. Parts of the apparatus *not* shown are: The *syringe holder* to which the syringes are clamped; the *cylinder and the metal piston* which guides the T piece driving the syringe pistons and supports the light beam slit; the *weighted table* to which the syringe holder is clamped; and the *padded mallet* used to drive home the syringe pistons and simulate systole. Also not indicated are the descending limbs of the aortic and pulmonary artery cannulas which go directly away from the reader, the side tubes on the same cannulas which would project directly towards him, and the pressure bottle attached to a side tube on the pulmonary artery cannula. The pressure bottle, shown in the figure, which is attached to the femoral artery is raised above the level of the artery to provide diastolic pressure.

APPARATUS

Figure 1 shows the general arrangement of our experiments.

A pair of 100 cc. glass Luer syringes were used to inject the fluid. The end of each, cut off by the glass blower, was replaced by a tightly fitting rubber cork perforated to contain a glass tube 1.8 cm. in internal diameter. The 2 syringes fitted side by side into a wooden holder into which they were firmly fixed by a yoke screwed down. Another set of screws bearing on a plate which fitted over the rubber corks and was perforated to admit the glass tubes, held the corks firmly in place in the end of the syringes.

The handle of the glass piston of each syringe was in contact with a single metal cross bar forming a "T" with a single metal piston which traveled through a long wooden cylinder firmly attached to the base of the syringe holder. The top of this cylinder was slit and through this slit projected a thin sheet of composition board, whose base was firmly set in the metal piston. In this sheet was the slit which provided the optical record of the position of the syringe pistons at every instant.

The syringe holder was clamped to a heavily constructed table containing a block of concrete in a compartment just below its top. We have not weighed the table but 2 men could lift it only with great difficulty. The long dimensions of the syringes were set at right angles to the long axis of the subject on the ballistocardiograph so that the movement of the pistons, and of the fluid in the syringes and cannulas, was at right angles with the line in which the ballistocardiogram was recording the forces and so did not affect this record until the fluid was turned into the great vessels.

Both cannulas were glass tubes 1.8 cm. in internal diameter. In the position used in the experiments the 1st limb of the aortic cannula extended horizontally 27 cm. from the point of attachment to the syringe. The tube was then bent to a right angle (the 1st angle) and extended directly downward for 16 cm. making the second limb. It was then bent to another right (the second angle) and the third limb extended 6 cm. headward to its tip. There was a slight constriction 2.5 cm. from the end for tying the cannula into the aorta. The corresponding limbs of the pulmonary artery cannula were 25, 11 and 5 cm. The first angle was also a right angle but the second angle was of 45° so that the third limb projected headward and downward, a position which better fitted into the pulmonary artery. This cannula was also provided with a constriction for tying it in place.

Both aortic and pulmonary cannulas had small side tubes of 5 mm. internal diameter at the first angle and the pulmonary cannula had a second side tube located near the syringe junction. The latter was attached to a perfusion bottle. During "systole" these side tubes were closed by rubber tubes and pinch cocks. This arrangement permitted clots to be washed out and bubbles to be caught and expelled from the system at the start of the experiments.

When in position the aortic and pulmonary artery cannulas were pushed hard against the end of the similar tubes emerging from the syringes and held in place by rubber hose connections.

Several smaller glass cannulas, from 4 mm. to 6 mm. in internal diameter, were made for insertion into femoral arteries; the largest which could be inserted was used. This was attached by a rubber tube to a pressure bottle filled with water or saline and set at, or above, a level corresponding to the diastolic pressure.

Either tap water or physiologic salt solution was used to fill the system.

A Hamilton manometer with a lead tube 70 cm. long was mounted on the wall beside the ballistocardiograph. Its period of vibration, when full of fluid was 150 per second. The needle, of 16 gage, was inserted into the root of the aorta.

The three optical recording systems were of the usual type, and the beams were directed into the moving film camera so that ballistocardiogram, blood pressure and ejection curve were recorded simultaneously on the same film.

In order to drive home the pistons and reproduce systole a number of devices were employed. A double pump driven by cams and an electric motor was built but it proved less satisfactory than simpler methods. Pushing the syringe pistons home with the hand provided smooth and satisfactory systoles, but by this means it was very difficult to secure the rapid initial acceleration which one expects from a normal heart, and we usually obtained ballistocardiograms abnormal in form. So these "hand systoles" were used to secure records when slow acceleration was desired. To secure more rapid acceleration we struck the metal piston with a mallet, heavily padded with sponge rubber to soften the blow. We first used a sledge hammer weighing 3 lb., supported by a fixed iron rod thrust through a hole bored in the handle so that the head swung on a radius of 30 centimeters. Later we used a very large wooden mallet designed for driving tent pegs and obtained from army surplus property. It weighed 15.5 lb. and the head was 20 cm. in diameter. Supported by an axle penetrating the handle, it swung on a radius of 90 cm. We had expected to pull the mallet back to a certain arc, and by dropping it, strike a measured blow, but we found we could secure smoother and more satisfactory curves by keeping the hand on the mallet head throughout the swing and pushing it home after the piston had been struck.

Material

Ten cadavers were employed. The first 4 were needed to develop a satisfactory technic and no records of value were obtained from them. The rest were:

1. February 5, 1947. L. Pe., female, age 48, weight 78 Kg., height 157 cm. Clinical diagnosis: Jaundice. Pathologic diagnosis: Postnecrotic cirrhosis of the liver. The heart, coronaries and aorta were normal.

2. February 27, 1947. H. W., female, age 14, weight 49 Kg., height 154 cm. Clinical diagnosis: Myasthenia gravis. She died suddenly and unexpectedly. Pathologic diagnosis: Heart normal, minimal atheroma of great vessels; no emboli or infarcts were found.

3. March 3, 1948. M. E., female, age 72, weight 78 Kg., height 163 cm. Clinical diagnosis: Arteriosclerotic heart disease. Urinary tract infection, uremia. Pathologic diagnosis: Heart 630 Gm., arteriosclerotic heart disease, mural thrombi both auricles and aorta. Thrombosis of both ovarian veins with extension into the renal veins, infarcts of left kidney, multiple emboli in lungs.

4. October 12, 1948. J. K., male, age 68, weight 50 Kg., height 156 cm. Clinical diagnosis: Lymphatic leukemia, syphilis. Pathologic diagnosis: Lymphatic leukemia, syphilitic aortitis with dilatation. No emboli, thrombi or infarcts.

5. November 15, 1948. M. M., female, age 46, weight 50 Kg., height 153 cm. Clinical diagnosis: Carcinoma of sigmoid. Pathologic diagnosis: Carcinomatosis. No emboli, thrombi or infarcts were found.

6. December 7, 1948. L. Po., female, age 38, weight 80 Kg., height 156 cm. Clinical diagnosis: Malignant hypertension (B.P. 260/140), cerebral hemorrhage. Pathologic diagnosis: Malignant nephrosclerosis, left ventricular hypertrophy, cerebral hemorrhage. No emboli, infarcts or thrombi.

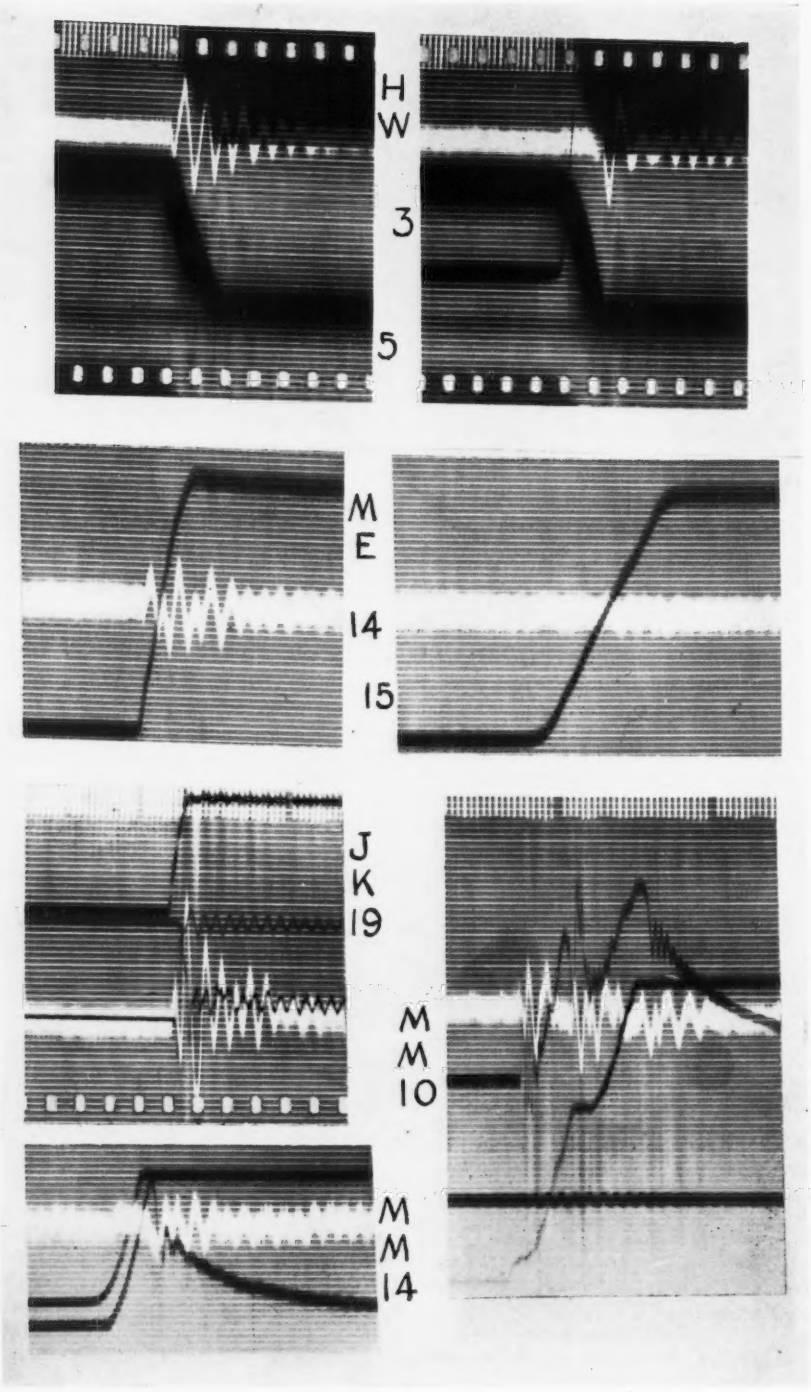

FIG. 2.

Conduct of Experiments

Whenever an opportunity presented itself, those members of the team who were available assembled at once. While the cadaver was in the morgue, the midline incision was made and the sternum removed. A large cannula was inserted: into the aorta only in the first two experiments, into the pulmonary artery only in the third; and cannulas were inserted into both vessels in the fourth, fifth and sixth experiments. These were tied firmly in place. A small cannula was tied in a femoral artery.

The cadaver was then taken to the laboratory and transferred to the ballistocardiograph. The weighted table was moved alongside and the injection and optical systems connected as shown in figure 1. Fluid was admitted from the perfusion bottles until all clots were washed out and all bubbles expelled through the side tubes which were then closed with strong pinch cocks. The needle of the Hamilton manometer was inserted into the aortic arch. Finally, the three optical systems were aligned and focused.

The perfusion bottle attached to the femoral cannula was hung above the subject at a level chosen to produce normal diastolic pressure in the aorta; in the early experiments, the elevation was 1 meter but in later ones, higher levels were used. When all was in readiness the pinch cock above this cannula was opened, allowing fluid to run into the femoral artery as fast as it would. An observer watched the beam indicating a rising pressure in the Hamilton manometer; when it leveled off he started the camera. After noting that everything was recording he signaled "Go" and one or both

Fig. 2.—Ballistocardiograms, Cardiac Ejection Curves and Aortic Pressure Records Secured Simultaneously. *Subject H. W.* (curves 5 and 3). Only the aorta was injected. Time above, the smallest interval = 0.04 sec. The white line is the ballistocardiogram, the heavy black line records the travel of the syringe plunger, falling as the syringe is emptied; the lighter black line shown only in the right hand figure is the blood pressure record. The amount injected was 84 cc. in each instance. Alignment is good. The record shown on the left was secured by striking the syringe plunger with the padded mallet, the record on the right, by pushing the plunger in by hand. Note that when the initial acceleration is rapid (left picture), the resulting "normal" ballistocardiogram resembles that found in healthy young adults; when the initial acceleration is slow (right picture), the ballistic deflection is very small until the syringe, stopping abruptly when it reaches bottom, causes a marked "stopping complex." Ballistocardiograms of this "abnormal" type are found in certain cases with hearts judged abnormal by other criteria.

Subject M. E. (curves 14 and 15). Only the pulmonary artery was injected. The time record, cut off, was similar to that of M.M. 10. The black line rises as the syringe is emptied. The injection was 68 cc. in both right and left pictures. Note that the slowly accelerated and decelerated injection causes little if any deviation of the ballistocardiogram.

Subject J. K. (curve 19). Both arteries injected. Black line above is the syringe record—it rises as the syringe is emptied; the black line next below is the blood pressure reference line; the third black line, at first superimposed over the ballistocardiogram is blood pressure at the root of the aorta; diastolic pressure = 30 mm. Hg, systolic = 75 mm. Hg. The alignment test shows the syringe record to be perfectly aligned with the ballistocardiogram; blood pressure is 0.04 second too far to the right. Note the sharp injection onset and the normal ballistocardiogram. Striking the syringe with the padded mallet imparted a vibration to our recording systems in this subject, this can be seen by the vibration in the blood pressure reference line as well as in the other records.

Subject M. M. (curve 10). A most irregular injection. Syringe record starts below and ends above all other black lines; 91 cc. was injected into pulmonary artery, 97 cc. into the aorta. Diastolic blood pressure was 102 mm. Hg; the peak systolic pressure reached 180 mm. Hg. Note the extremely irregular injection curve. The ballistocardiogram which at first glance seems hopelessly confused, on close inspection is seen to be deflected normally by the repeated starting and stopping of the injection curve, which also affects blood pressure profoundly. Alignment as in M. M. 14.

Subject M. M. (curve 14). Time as in M. M. 10. Upper black line, syringe record, a smooth injection accelerated rather slowly. Thirty-nine cc. were injected into the pulmonary artery, 41 cc. into the aorta. The diastolic blood pressure at the root of aorta was 90 mm. Hg, the systolic 140 mm. Hg. Note the normal blood pressure contour with ballistic aftervibrations appearing after the diastolic notch and the suggestive, but incomplete similarity between ballistic deflections and pressure waves. Alignment test shows blood pressure record to be 0.04 sec. too far to the right, the syringe record to be displaced 0.05 sec. to the left of the ballistocardiogram.

syringe pistons were shoved home. When the light beams came to rest the camera was stopped, the syringes refilled from the perfusion bottles and the systole repeated. The amount of fluid injected, and the shape of the ejection curve were varied as much as we could. The number of such systoles was limited only by the length of time the cadaver was available.

The cadaver was then sent back to the morgue where the position of the cannulas was verified and the vessels carefully inspected for obstruction by clots and for lesions of the vascular system. The necropsy was then completed in the usual manner. Meanwhile, in the laboratory, the manometer and the syringe records were being calibrated, the ballistocardiogram having been calibrated before as well as after the experiment. Tests for alignment of the light beams completed the experiment.

Analysis of the records. The records of the syringe piston position, the "cardiac ejection curve," were measured by a microscopic measuring machine known as a Keith-Lucas Comparator.* Various systems of measuring were tried, and a magnification of 12.5 diameters proved most satisfactory. The X-axis, time, was measured from the measuring engine scale; the Y-axis was read at each interval of time by counting the millimeter lines on the-record photograph and interpolating to 0.1 mm. The accuracy of this procedure was determined by remeasuring the first two points of each curve after an interval long enough for the operator to forget the previous reading; the test-retest correlation was 0.99. We started by measuring the curves at intervals of 0.02 second but intervals of 0.04 second proved more satisfactory, and all the curves reported here were measured this way. Hence, we recorded the position of points on our curves at each 0.04 sec. intervals.

In reading ballistocardiograms, the time of the peaks and valleys was identified exactly with the measuring engine scale but the depth and altitude of the waves was read by the naked eye, as ballistocardiograms are usually read, for we wished to include the error of thus reading them in our calculations. Also, the edge which seemed sharp to the naked eye was often blurred when magnified and it was doubtful whether magnification permitted greater accuracy. In accord with our practice in the clinic, distances were read to the nearest millimeter, the half being used occasionally when there was doubt as to which value should be chosen. These peaks and valleys were plotted and joined by straight lines, which represent the record with sufficient accuracy.

After measurement both ballistocardiograms and the ejection curves were plotted on cross section paper, 0.2 inch representing 1 mm. on the photograph and 0.04 second. The differentiations were performed as shown in figure 3 and the integrations as shown in figure 6.

The blood pressure curves were not analyzed in detail and we contented ourselves with recording systolic and diastolic pressure.

The mathematical analysis was performed by Dr. Starr and Dr. Horwitz with the technical assistance of Mrs. M. W. Murray.*

Results

Good records when the injection was *into the aorta only* were obtained in eighteen, thirteen and four "systoles" in Experiments 1, 2 and 4, respectively. When the injection was *into the pulmonary artery only*, good records were secured in sixteen and six "systoles" in Experiments 3 and 4. When both arteries were injected simultaneously, ten, twenty-six and

* Made by the James G. Biddle Company, Philadelphia, and made available by Dr. H. C. Bazett.

* Because of the great labor involved in the mathematical computations described here and in other parts of this paper we investigated the use of the differential analyzer in the Moore School of Electrical Engineering of the University of Pennsylvania, and we are indebted to Mr. George W. Patterson for instruction and advice on this subject. The three integrations could be readily performed by this instrument but it would take considerable time both to set up the analyzer for the solution of our particular problem and to convert our curves into a form suitable for use in the analyzer. It was concluded, then, that this instrument would not be of great aid at this stage of our work and the computations were performed with the assistance, first of a Monroe, and later of a Marchant calculator.

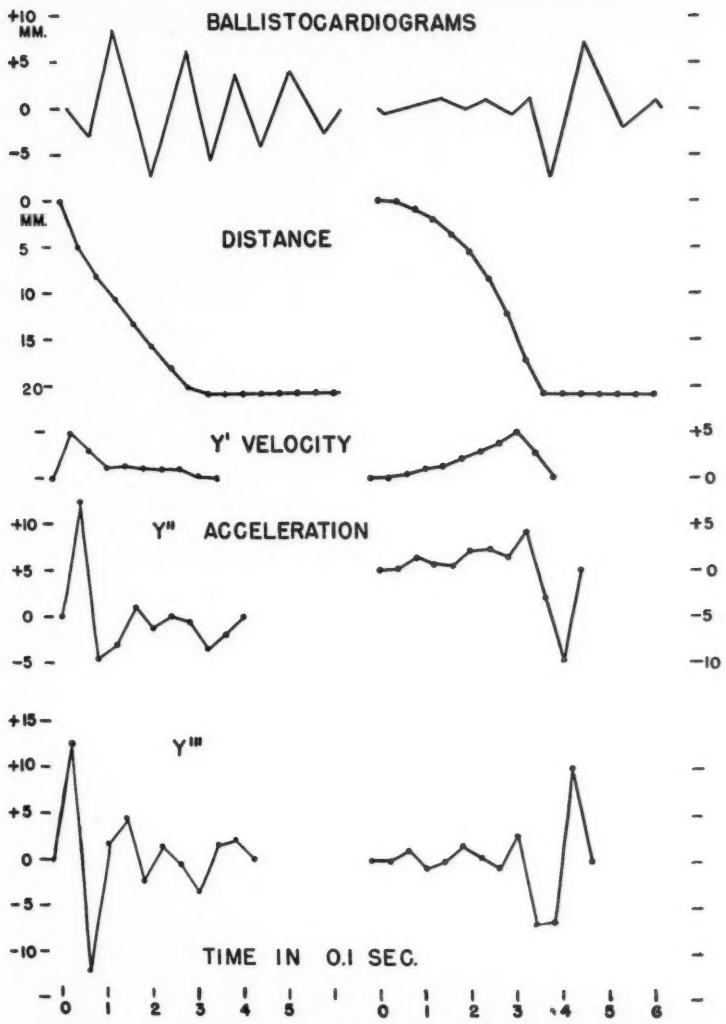

FIG. 3.—Two Ballistocardiograms and the Corresponding Cardiac Ejection Curves with Three Differentiations of the Latter. *First Row:* Left, a plot of the ballistocardiogram of J. K., curve 5 (see fig. 2); right, of J. K., curve 3 (fig. 2). The scale indicates millimeters of deflection on the photographic record. The calibration showed that 280 Gm. displaced the light beam 1 cm.

Second Row: The cardiac ejection curves corresponding to the ballistocardiograms above them. The scale indicates millimeters of deflection on the photographic record. The calibration indicated that a movement 1 mm. on the photograph corresponded to the ejection of 4 cc.

Third Row: The first derivatives of the cardiac output curves given above them made with a Δ time of 0.04 sec. These curves, therefore, are plots of velocity against time. The scale (right) is the same as in the row above; i.e., 1 unit corresponds to 1 mm. deflection on the photograph and so to an ejection velocity of 100 cc. per sec.

Fourth Row: The second derivative, acceleration. The scale, otherwise making the drawing too small, has been arbitrarily increased by a factor of 2.5. Therefore, one unit on the scale equals an acceleration of 1000 cc. per second.^{2}

Fifth Row: The third derivative of the cardiac output curve, or the first derivative of acceleration. The scale is the same as for the second derivatives in the fourth row, so that one unit equals a rate of change of acceleration of 1000 cc. per sec.^{2} each 0.04 second.

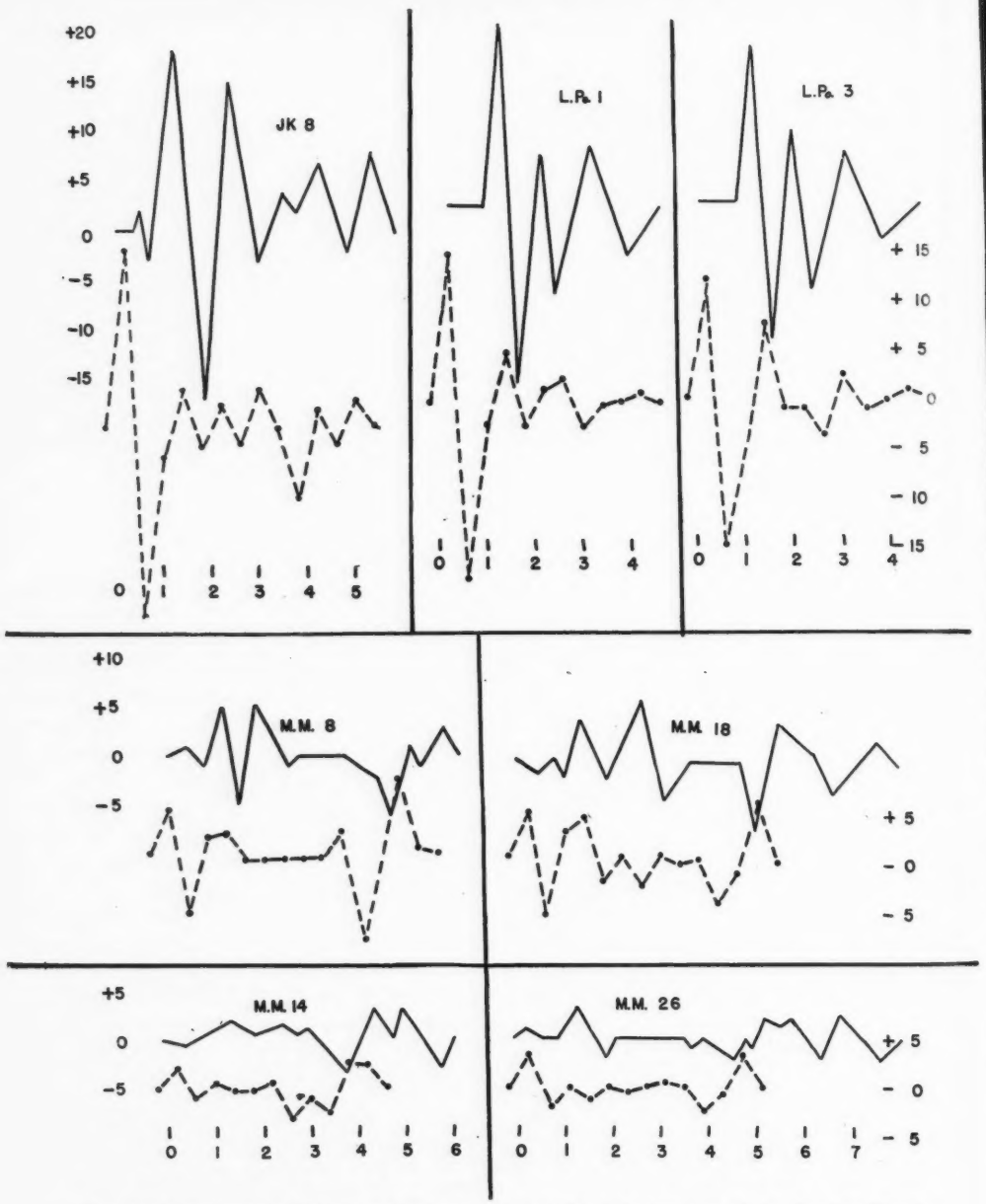

FIG. 4.—Miscellaneous Ballistocardiograms and the Third Derivatives of the Cardiac Ejection Curves which Generated Them. Solid lines equal ballistocardiograms. Their scale is to the left, 1 unit = 1 mm. deflection on the photographic record. (1 mm. deflection = 28 Gm.) Broken lines equal third derivatives calculated as shown in figure 3. Their scale is to the right; 1 unit = a rate of change of acceleration of 1000 cc. per sec.^{3} in each 0.04 second.

six good records were secured in Experiments 4, 5 and 6, respectively.

Typical records are illustrated in figure 2, and, as the results can best be described with

the record before one, the legend of this table has been made unusually ample, and the description in the text will be brief.

A comparison between the ballistocardiogram and the calculated third derivative of the cardiac ejection curves in seven typical systoles are given in figure 4. When inspecting these results one must recall that artefacts of 1 mm. or less, due to extraneous causes such as the movements of the elevators in the building, are seen in many ballistocardiograms and exact correspondence with the theory must not be expected.

Other results of the mathematical analysis will be found in the tables, where correlation coefficients and formulas of regressions, with standard deviations about them, are given. This analysis was designed to explore the relationship between the deflections of the ballistocardiogram and the forces generated by the heart. This relationship has proved to be close.

Discussion

We chose our method of attack for a reason that was, to us, compelling. It promised that both the cardiac output and the form of the cardiac ejection curve could be measured with an accuracy not yet approached in experiments on living men or animals, and we believe that this goal has been attained. But the question must certainly be raised whether results obtained soon after death would provide knowledge applicable to conditions in the living.

A chief reason for the belief that results obtained in our fresh cadavers may be applied to the living is the similarity of the ballistocardiograms in the two conditions. The sizes and patterns we find in the living we can produce in the cadaver subjects. It is true that with the cannulas described, the I wave tends to be smaller in relation to J than is usual in the clinic, but using cannulas with a longer third limb entirely corrects this. It seems easy to explain why recent death does not change the records. Independent of metabolism, which ceases at death, the ballistocardiogram records forces generated within the body, and it would be distorted only by changes in the physical properties of the body which would interfere with the normal transmission of such forces. Physiologists in the past have not hesitated to apply measurements of aortic elasticity made after death to conditions existing in living subjects; nevertheless, the problem presented must be carefully considered.

Tapped once on the head, a living subject on the ballistocardiogram undergoes a series of damped vibrations which are easily identified between systolic complexes, especially when the pulse rate is slow. Similarly tapped on the head, fresh cadavers undergo vibration at the same average rate[1]; the cadavers of our present series behaved similarly. Interruptions by cardiac forces make it hard to estimate the degree of damping with accuracy in the living and the comparison is rough, but certainly the damping does not appear to differ materially in the two conditions. Judged by their vibration properties, the body tissues in our experiments did not seem to have greatly changed since death.

Further assurance was sought by a study of the pressure volume relationships. In our cadavers, after the diastolic blood pressure had been brought to normal, the smooth injection of a normal stroke volume into the aorta gave a perfectly normal pressure curve, with a normal dicrotic notch. Figure 2 gives an example. It is true that in some of our records, vibrations unfamiliar to those accustomed to peripheral pulse records appear on parts of the pulse wave, but this is to be expected in pressures taken from the aortic arch; it was found in animals by Frank.[4] With the diastolic and systolic pressures normal and the pulse wave of normal contour, the aortic elasticity seems to have been essentially normal in our experiments. We did no similar experiments on the pulmonary artery but we believe that normal elasticity, demonstrated in the aorta, can be safely assumed for the pulmonary artery.

As far as we can detect, the physical properties of the body on which our method depends are essentially normal in our fresh cadavers; hence, we regard this type of preparation as suitable for many kinds of physiologic experiments. We do not, however, wish to minimize the unusual difficulties inherent in experiments of this kind, and these will now be discussed in detail. Some of these difficulties would apply

to any type of physiologic experiment performed in fresh cadavers; others pertain only to our special interests.

Difficulties and uncertainties. Every effort was made to obtain material as fresh as possible but some time elapsed after death before necropsy permission could be secured and after this was obtained the apparatus took considerable time to set up. Thus, slight rigor mortis had sometimes set in before the experiments could be begun. Also the time at our disposal was strictly limited by commitments to have the necropsy completed by a certain time. In addition, the normal interests of the pathologic department, the concern of clinicians to verify or disprove their diagnoses and the use of necropsies for teaching created demands on the available material which rightly had precedence over our highly unorthodox interests. There was a fear, which experience showed to be not well founded, that repeated injections of water or salt solution might spoil the tissue sections by making the tissue edematous, and so might interfere with the routine pathologic studies. Such difficulties account for the fact that we had but ten opportunities to work in two and one-half years. Indeed, it was only because of most helpful cooperation from many people and the fact that Dr. Starr's laboratory was located within the hospital near the morgue, that this type of work was possible at all.

Other difficulties pertained to our particular problem but many proved less than we had anticipated. We feared that postmortem clots would obstruct the aorta and pulmonary artery, and that we should find it impossible to dislodge them, but the completion of the necropsy always showed all large vessels to be clean and unobstructed.

We feared that when the syringes were struck by the padded mallet there might be a direct mechanical transferrence through the building to the record, and the weighted table was designed to prevent this. We studied striking the table directly and this imparted almost no vibration to the record. In Experiment 4, however, there was undoubtedly direct transference of the shock of striking the syringes to all the records when the blow was strong, for the manometer reference line was thrown into vibration, as was the blood pressure record, and the shock tended to change the ballistocardiogram's base line slightly. Figure 2 shows such a record. Such effects had not appeared in previous records, nor did they recur in any subsequent experiment; hence, unable to reproduce the difficulty, we were forced to the belief that in Experiment 4 the heavy table had been so placed that an unusual harmonic in the building had been created, the blow starting vibrations which were transmitted through the table and floor, to the wall on which the mirrors were mounted.

We expected that findings when the necropsy was completed would throw light on our errors and perhaps cause us to discard experiments. The lungs, collapsed throughout the experiments, were often noted to contain excess fluid. In Experiment 3, multiple emboli were found in small pulmonary vessels. In all experiments, however, the great vessels were found normal or nearly so, and in the belief that the ballistocardiogram depends on the movement of blood in these vessels, we did not discard any results secured because of abnormality discovered in the tissues or small vessels.

Other difficulties were surmounted by a gradual improvement in apparatus and technic. We soon found that to produce normal ballistocardiograms we must have an injection technic that gave rapid acceleration early in systole and gradual deceleration in the latter part. When systole was produced by pushing the syringes with the hand the results were just the reverse, velocity increasing gradually and stopping with a jerk when the syringes hit bottom. Figure 3 (upper right) gives an example of this, and the records were highly informing, though the abrupt cessation of ejection was probably not analogous to anything that occurs during life. The use of the padded mallet secured the rapid initial acceleration we desired and a rubber cushion—together with the development of sufficient skill—enabled us to stop the moving pistons gradually and without hitting bottom with a jerk.

Occasionally, we had difficulty getting smooth ejection curves because of some sticking of the syringe pistons in their barrels, or fric-

tion between the metal piston and its cylinder; occasionally the padded mallet, if struck slightly obliquely against the metal piston slipped and caught again, so that bizarre curves were sometimes obtained. Figure 2 shows the record of a systole in which this happened twice. Although we regarded these as failures at the time of the experiment, the records of such "abnormal systoles" proved of great value in the study of the genesis of abnormal ballistocardiograms.

We attempted to keep the diastolic pressure at a normal level and usually succeeded, but until the calibration at the end of the experiment the height of this pressure had to be estimated roughly from the position of the light streak. In Experiment 4, this estimation was incorrect and the diastolic pressure was always lower than normal.

We found it difficult to secure two 100 cc. glass syringes of exactly similar diameter so that a difference of a few cc. often appeared in the amount injected simultaneously into the aorta and pulmonary artery. We do not doubt that differences of this amount occur normally during the respiratory cycle, and mention it only to account for the small differences given.

Finally, in contrast to the struggle of securing the material and of setting up the elaborate apparatus in a great hurry, once all was in order the experiments presented no difficulty. "Systoles" of all kinds and types were then run off with ease and dispatch. A few of these records could not be analyzed because the beams ran off the film, or coincided or were too faint to be read, but we discarded none for any other reason. This study is based on 97 satisfactory records of these artificial systoles.

The relation between the ballistocardiogram and cardiac function. We believe that the records shown in figure 2 and that the transcriptions and calculations given in figures 3 and 4 are a fair sample of our data. Inspection of these figures, and indeed of the data as a whole, leads to the apparently inescapable conclusion that there is a mathematical relation between the curve of cardiac output at every instant and the ballistocardiogram, that the latter is related to the third derivative of the former, and that the deflections of the ballistocardiogram follow the curve of the cardiac output by a brief interval in time. This relation holds despite large differences in aortic pressure; the systolic pressure varied from 75 to 180 mm. in our experiments.

To this last statement certain reservations must be made, and the first is concerned with artefacts. Since aftervibrations follow a single blow delivered experimentally[1] we have every reason to expect that a force delivered early in the cardiac ejection curve will set up similar aftervibrations which will cause the latter part of the record to deviate from a true account of the forces then present. Close inspection of the records (figures 3 and 4) shows clearly that this is the case. When no strong force is applied early in systole (as in records shown in figure 3, upper right, and figure 4, M.M. 14 and 26), the ballistocardiogram late in systole corresponds closely to the third derivative of the ejection curve, but if there is a strong force early in systole (figure 3, upper left, and figure 4, JK 8, L.Po 1 and 3), its aftervibrations cause the latter part of the record to deviate from the forces then present. We have, therefore, confirmed the original concept[1] that the part of the curve recorded early in systole will often give a better representation of the forces which originate it than will that recorded later.

The second reservation is emphasized by the fact that a single differentiation of the cardiac ejection curve does not account for the I wave of the ballistocardiogram. The reason for this seems clear and will be discussed later.

Despite these reservations, by our technic of injecting the vessels we produce a ballistocardiogram which, when the I wave is neglected, is surprisingly similar to the simple third derivative of the injection curve. We believe that we see the reason for this relationship and that it can be best explained, nonmathematically, by a simple analogy:

Figure 5 shows a man in a small suspended room, the room free to move in the plane of the printed page, but this movement is restrained by a spring. The movement of the room represents the ballistocardiogram. The man within the room is leaning back against

the wall and has the nozzle of a hose in his hand, this is attached to a pressure tank on the floor beside him. At *A*, all is in equilibrium: the nozzle is closed, no water is flowing, and no forces are being exerted. At *B*, the man has opened the nozzle, the stream has started but as yet it has not reached the opposite wall. At this instant the jet effect due to acceleration of the fluid entering the nozzle drives the man backward and the room is pushed to the reader's right. This effect persists until, as at C, the stream of water reaches the wall opposite. Then the force exerted at the nozzle is neutralized by that now exerted against the wall, equilibrium is restored and the spring returns the room to its original position. The man now opens the nozzle wider. Again for a brief interval, as in *D*, the force developed at the nozzle exceeds that against the wall, and so the room moves again to the reader's right. As soon as the increased stream strikes the opposite wall, the forces balance once more and equilibrium is again restored. If the man now diminishes or stops the stream, the force against the wall exceeds that at the nozzle for a brief period, as at *F*, and the room moves to the reader's left until the end of the diminished or stopped column of water reaches the wall, when equilibrium is again restored.

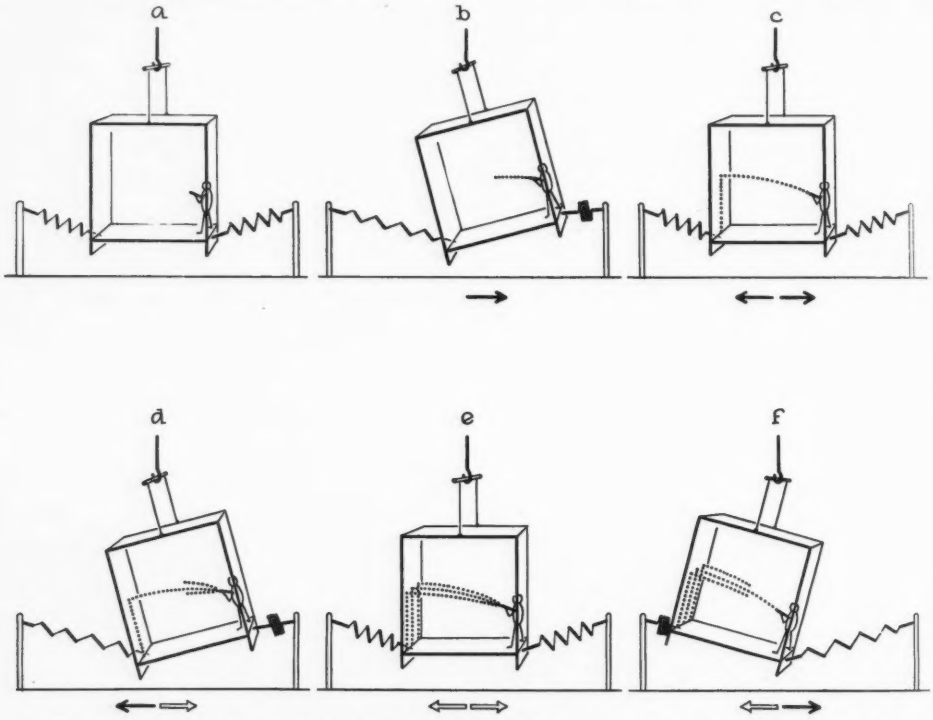

FIG. 5.—Schema to Illustrate the Reason why the Ballistocardiogram is Related to the First Derivative of Cardiac Force and so to the Third Derivative of the Cardiac Ejection Curve. For full description, see text. The arrows under each picture indicate the direction and size of the forces developed when the stream of water is increased and diminished.

This analogy makes plain the fundamental fact that must be grasped to understand the ballistocardiogram: the room is moved by forces which escape neutralization within it. The magnitude of these escaping forces depends on the rate of change of the force generated at the nozzle, the amount of increase (or decrease) which takes place in the time interval required

for the stream to cross the room. Thus, the room is moved by the first derivative, the rate of change of the force; force is the product of mass times acceleration, the latter the second derivative of the fluid displacement curve in time. Thus, the movement of the room, and the ballistocardiogram are related to the third derivative of the cardiac ejection curve.

This analogy is, of course, an oversimplification and it explains only two of the three main waves of the ballistocardiogram. Instead of the man simply squirting the hose, as in figure 5, he should squirt through a curved tube with collapsible walls. The point may be better comprehended by thinking of figure 5 as representing the happenings in the long thoracic and abdominal aorta. To visualize the happenings in the heart, ascending aorta and pulmonary artery, one may think of a second man with a second hose, pointing the nozzle in the opposite direction towards the wall on the reader's right with the nozzle tip only a short distance away from this wall. His stream of water is larger than that of the first man, but as the time taken by the stream going from nozzle to wall is much shorter, because the distance is shorter, proportionately less energy will escape to move the room than when the course is longer. This new man opens his nozzle a little before the man pictured in figure 5 and as the jet starts, the escaping forces move the room first to the reader's left, the I wave, and as the jet diminishes, to the right, contributing to the J wave. As the stream of the new man reaches the wall the man pictured opens his nozzle. The starting of his stream contributes to the J wave, its stopping makes the K wave. Thus, the clinical ballistocardiogram is not an exact reproduction of the third derivative of the cardiac ejection curve; it is the algebraic sum of two third derivatives of this curve of opposite signs, one placed a little before the other in time.

The bearing of the new data on our former concept. In the early reports,[1, 2] the ballistocardiogram was related to the second derivative of an assumed cardiac ejection curve. A family of such curves, moved serially in time, and added or subtracted from one another according to sign, gave a result which in many ways resembles that now secured by once more differentiating the original curve. The old theory failed to account fully for the "K" wave, which was accordingly regarded as largely an artefact, an overswing from the immediately preceding J wave. However, as soon as clinical studies had begun[5] we encountered patients with cardiac disease whose ballistocardiograms showed a K wave the depth of which far exceeded the height of the preceding J wave; this idea, then, was abandoned. Also, Hamilton and coworkers[3] have supplied evidence that not only the K wave but also the waves which follow it represent forces. Our new data completely supports this contention; indeed, the ballistocardiogram is proving to be much closer to a true record of the forces than we originally believed possible.

It is interesting that in the clinical studies, our practice has not been inconsistent with the finding that the ballistocardiogram is related to the third derivative of the cardiac ejection curve. By calculating cardiac output by the area method, we integrated the ballistocardiogram, the result then being related to the second derivative, acceleration, and hence to cardiac force. Our cardiac output method was based on the assumption that the heart's output would be proportional to the force exerted, and in normal conditions, when the ballistocardiogram is normal in form, this appears to be generally true.[6] In preferring the area method to the altitude method (both described in the first paper), we were proceeding in the right direction, though for incompletely understood reasons. For a rough, quick and easy method of estimating cardiac output we have no improvement over the area method to suggest at this time. A preliminary report on its accuracy has already been published[7]; the study reported in this paper, chiefly concerned with abnormal ballistic forms and lacking a large number of "normal" records, does not permit a final standardization against absolute values at this time. The original concept[1] that cardiac output is underestimated by our formula when the ballistic form is abnormal has been completely verified.

Another conclusion drawn from our original theoretic concepts[1] was that the form of the

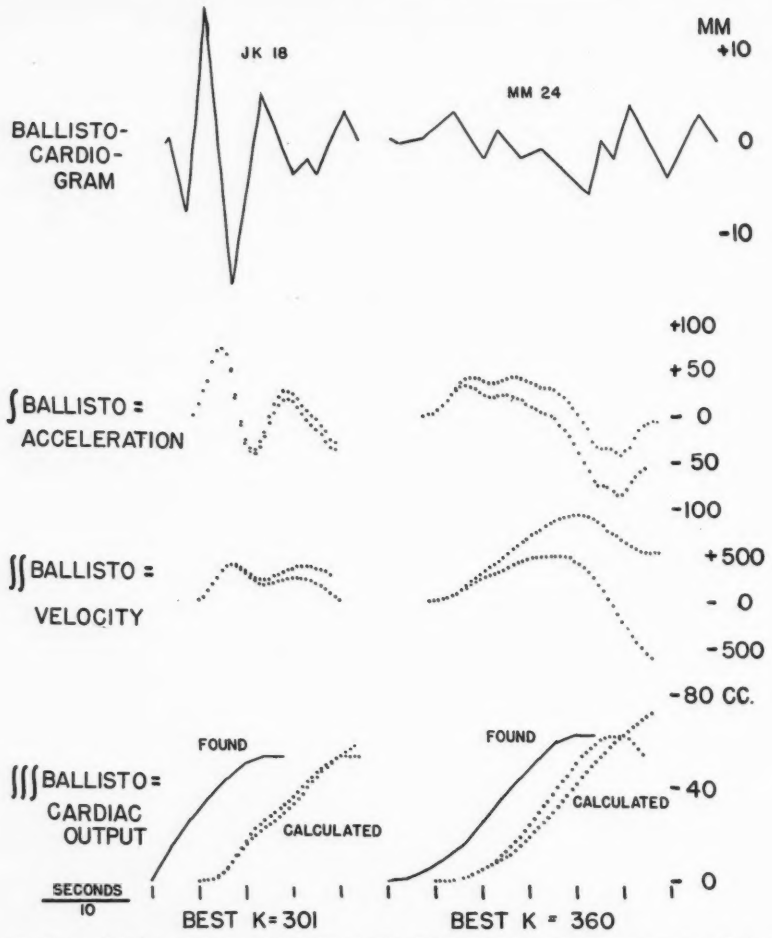

FIG. 6.—Repeated Integrations of Two Dissimilar Ballistocardiograms Compared with the Corresponding Cardiac Ejection Curves. The scale to the right of the ballistocardiogram records the deflection of the record in mm. from the base line selected. The calibration 1 mm. deflection = 28 Gm. = 27,440 dynes.

The integrations were all performed with a Δ time of 0.01 sec. by plotting and counting squares. The integrations were started where the I – J lines of the ballistocardiograms crossed the base line. Two base lines were used in integrating each ballistocardiogram and the two integrals which resulted are plotted together to permit comparison. They start close together but diverge considerably.

The scale to the right of the first integral indicates the sum of the units (squares) at each instant of time. Each of these squares represents an area 1 mm. $\times$ 0.01 sec. The scale to the right of the second integral also indicates the sum of the units (squares) at each interval of time. Each of these squares now represents an area with dimensions of (1 mm $\times$ 0.01 sec.) $\times$ 0.01 sec. The scale to the right of the third integral (dotted line) pertains primarily not to it but to the cardiac ejection curve (solid line) which stands beside it. This scale is in cc. ejected and it was obtained from the calibration of the syringes. The plotted third integrals have been fitted to this scale by setting their ends to bracket the total amount ejected.

The third integrals were estimated, as were the first two integrals, as sums of squares, each in this case with an area with dimensions of [(1 mm. $\times$ 0.01 sec.) $\times$ 0.01 sec.] $\times$ 0.01 sec. To make the calculated curve fit the scale determined, the sum at each instant of time was divided by a factor

ballistocardiogram depended on the form of the cardiac ejection curve. The evidence for this now amounts to proof, for by varying the form of the ejection curves we produce corresponding changes in the resulting ballistocardiograms. Most of the abnormal forms seen in clinical records can now be reproduced at will, so that the knowledge of their genesis has been greatly advanced by the experiments reported here. Even when the ejection curves are, by accident, most irregular, as in that recorded in figure 2, MM10, the ballistocardiogram still follows the forces. Hence many, but by no means all, of our original ideas have been verified.

In addition, the new data have stimulated new lines of thought. We are now in a position to raise our sights, to attempt measurements of cardiac function of a type impossible by other methods and, of the greatest importance, to measure the accuracy of any new scheme we may set up.

Estimation of the cardiac output at every instant of systole by integrating the ballistocardiogram. The demonstration of a close relationship between the ballistocardiogram and the third derivative of the cardiac ejection curve raises the question of whether this curve, the cardiac output at each instant of systole, cannot be estimated by integrating the ballistocardiogram three times. In this connection one should recall Abramson's[8] attempt to estimate cardiac output *per beat* from the second integral of the ballistocardiogram. Figure 6 depicts a test of the idea by integrating two experimentally produced ballistocardiograms completely different in form; the legend gives the mathematical details. The problems which presented themselves were as follows:

The first concerned the point on the ballistocardiogram when integration should be started. A natural place to begin is the point where the H-I line of the ballistocardiogram crosses the base line. Then, when the integration of the I wave has been completed, one should reverse the sign and proceed to integrate the J wave, and the rest of the curve in the usual manner, the reversal of signs allowing for the difference in direction of the flow of blood rounding the aortic arch. A more simple procedure is to neglect the I wave and to start the integration where I-J crosses the base line, and this was used in the examples given (figure 6). For some curves, we used both starting places and the final results were not very different.

The second problem is when to stop the integration. We added the duration of systole to the time of our starting point and stopped there.

The third problem is concerned with the selection of the base line, and this is critical as it makes considerable difference in the results. We proceeded by trial and error, selecting what appeared to be the best base line by inspection. If the first integral did not return to zero when systole was over, as acceleration certainly should, we moved the base line up or down and repeated the primary integration, seeking a curve which returned close to zero or two curves whose ends bracketed it. The second integration, leading to velocity, was handled the same way. At the end of the third integration the curve should remain horizontal or fluctuate about a horizontal line; if it continued up or turned down, the choice of the base line was questioned. Usually we had to be satisfied with curves whose ends bracketed the situation we desired. Thus, in figure 6 (lower right), the true third integral obviously lies between the two dotted lines. We proceeded, therefore, until we secured base lines that most nearly satisfied us, and the same base line was always used for the first,

which proved to be 301 for the curves on the left and 360 for the curves on the right. If our accuracy was such that this figure had proved to be a constant for all curves, then the cardiac output at every instant could be estimated accurately from the third integral of the ballistocardiogram. The fact that the factors needed did not agree well indicates the uncertainty of the procedure. But it should be noted that the third integral reproduces the contour of the ejection curve with considerable accuracy. At one place, the start of the third integrals on the left, the calculation is more accurate than the measurement, for on close inspection under the microscope the gradual start could be seen clearly, though it was not recorded by measurements made every 0.04 sec. and so does not appear on the solid line.

second and third integrals. Moving this line as little as 0.25 mm. often made a large difference in the resulting curves.

Finally, there is the problem of giving absolute value to the coordinates of the third integral. In our experiments, the cardiac output being known, the factor needed can be estimated. In the examples in figure 6, it was 1/301 and 1/360. The average value which would be applicable to any ballistocardiogram appears to be approximately 1/300 but after integrating ten experimental curves according to the method given we found that the scatter was very great; in one curve, moving the base line 0.5 mm. changed the factor ten-fold. The uncertainty is increased by the repeated integration, and small errors are greatly magnified. For this reason we cannot advocate the triple integration of the ballistocardiogram as a practical method of estimating the cardiac output quantitatively at this time. On the other hand, the contour of the cardiac ejection curve is attained quite accurately by triple integration, and the examples given in figure 6 are typical of our other experience.

Estimation of cardiac strength. Our results demonstrate clearly that the ballistocardiogram is more closely related to the heart's force than to its output, so that estimates of force should be more accurate than these of output. This knowledge dates from the first publication,[1] but at that time an estimate of the heart's force from the ballistocardiogram, without any means of testing its accuracy, would have been little more than idle speculation. The efforts were then directed towards the estimation of cardiac output, a field in which the results could be compared with those secured by other methods and thus in some measure the correctness of our ideas could be tested, despite the fact that the absolute accuracy of the available cardiac output methods was unknown. Obviously we are now in a position to test our ideas against measurements with a far greater reliability and may properly ask ourselves questions unanswerable before.

Consider how cardiac force might be estimated from the ballistocardiogram, and how the error of such a method could be ascertained. Our experiments permit comparison between two forces; first, the cardiac force, or rather that portion of its energy output expended on moving the blood; and second, the force tending to move the body which is recorded by the ballistocardiogram. This second force can be directly calibrated in grams or dynes by noting the deflection of the light spot when a known weight moves the table. Therefore our data show that

$$\frac{d}{dt}\,(\textit{Cardiac Force}) = K\ \textit{Ballisto Force} \qquad (1)$$

Since any force = Mass × Acceleration

$$\frac{d}{dt}\,(MA) = K\ \textit{Ballisto Force} \qquad (2)$$

and

$$MA = K \int \textit{Ballisto Force}\ dt \qquad (3)$$

The results have put us in a position to compare ballistocardiograms with the forces required to produce them. We are not yet ready to calculate the "cardiac" force in absolute units, but it can be estimated in relative terms if one makes an assumption regarding *mass.*

Mass is not the cardiac output because blood is pushed on ahead of that leaving the heart; it is not the total blood volume because, the vessels being elastic, this is not moved as a unit at any instant. We need to know the mass accelerated at every instant of systole and a quantitative estimate of this seems far beyond us. Indeed, mass might vary with time, but the good correspondence throughout systole between the ballistocardiogram and the first derivative of acceleration indicates that mass is a constant for any subject; hence, we propose to handle it as such.

We estimate acceleration in the syringes, not in the great vessels, and as the latter may be of different diameters in different subjects, acceleration in the vessels may be different from that recorded by an amount which differs with each subject. However, the product of *mass* × *acceleration* will be the same in the syringes as it is in the vessels injected, for this product is independent of the diameter of the vessels.[9] The length of the vessels, however, is a factor in the situation, and should be taken into account in the calculation of force from our records of acceleration. Obviously, to obtain the vessel length of any subject

during life the best assumption is that the length of the vessels will be proportional to the length of the body; the sitting height might be better but it was not measured for our subjects. We propose, therefore, to calculate the force imparted to the blood, in relative terms, by using the acceleration derived from our records and a factor for mass which varies directly with the height of each subject. As it happens, our subjects are very nearly the same height; 5 of the 6 being between 153 and 157 cm. tall, so that the effect of this adjustment is less than random errors for most subjects. We believe, however, that this factor for mass should be employed and that in interpreting records obtained on children its importance might be great; we cannot hope to obtain evidence either to support or disprove the conception from our present data.

Having decided on what seems the best method for calculating force the next question concerns what aspect of the heart's energy output can best be estimated from ballistocardiograms and also what measurement may be most rewarding. From previous work on assessing the strength or weakness of the human heart, an attractive goal for the first attempt seemed the estimate of the maximal force delivered in any systole, a cardiac characteristic that is surely closely related to the concept of strength and weakness. We therefore searched for some aspect of the simultaneous ballistocardiograms that would permit us to estimate the maximal force delivered in any systole.

Many considerations inclined us towards using the spread of the record, as measured by I and J waves, for this purpose: first, to produce normal ballistocardiograms in our experiments the maximal force was delivered early in systole and these waves immediately followed; second, the general correspondence between the spread of ballistocardiogram and the force delivered was perfectly apparent even at the experiments themselves (when the operator struck a hard blow with the mallet the ballistocardiograph light spot was widely deflected, while a soft blow moved the spot but little); third, clinical experience has shown that in healthy young adults the I and J waves are large, while in many patients with chronic heart disease, especially elderly persons with long standing coronary heart disease, these waves are small or absent; fourth, the I and J waves occur early in systole where the ballistocardiogram reflects the forces most accurately; and finally, if one employs the sum of heights, or areas of two waves on opposite sides of the base line, the error of misplacing the base line is avoided or minimized. We therefore studied the correlation between several aspects of the I and J waves and the maximal force of cardiac contraction, the peak of the acceleration curve multiplied by a constant, M, corrected for body length. Tables 1 and 2 and figure 7 give the results. In order to express the estimates of maximal force, given in the vertical coordinates in figure 7, in per cent of a standard value, we have selected the force yielding ballistocardiograms of the average size found in healthy young men and arbitrarily placed it at 100 per cent.

The simplest measurement, the spread of the ballistic record or the vertical distance between the valley of I and the peak of J, was tried first. The correlation, $r = 0.93$, was excellent. Then, because the corresponding dot diagram (fig. 7, *A*) suggests slightly that the regression might be curved, we correlated our estimate of force with the square root of this same measurement on the ballistocardiogram. Again, the correlation, $r = 0.93$ is excellent, but not better than the first estimate.

Finally, because our results (Equation 3) suggested that the ballistocardiogram should be integrated before comparing it with cardiac force, we studied the relationship between the sums of the areas of the I and J waves and the corresponding estimates of maximal force. The dot diagram (fig. 7, *C*) showed plainly that this regression was curved; hence we correlated with the square root of these areas which significantly improved the scatter (fig. 7, *D*). The correlation, $r = 0.83$, is again highly significant but it is proved by Fisher's z test[10] to be definitely poorer than those secured by using the altitude of the waves.

Obviously there is a close relation between the spread of the ballistocardiogram and the maximum cardiac force; indeed it is a little

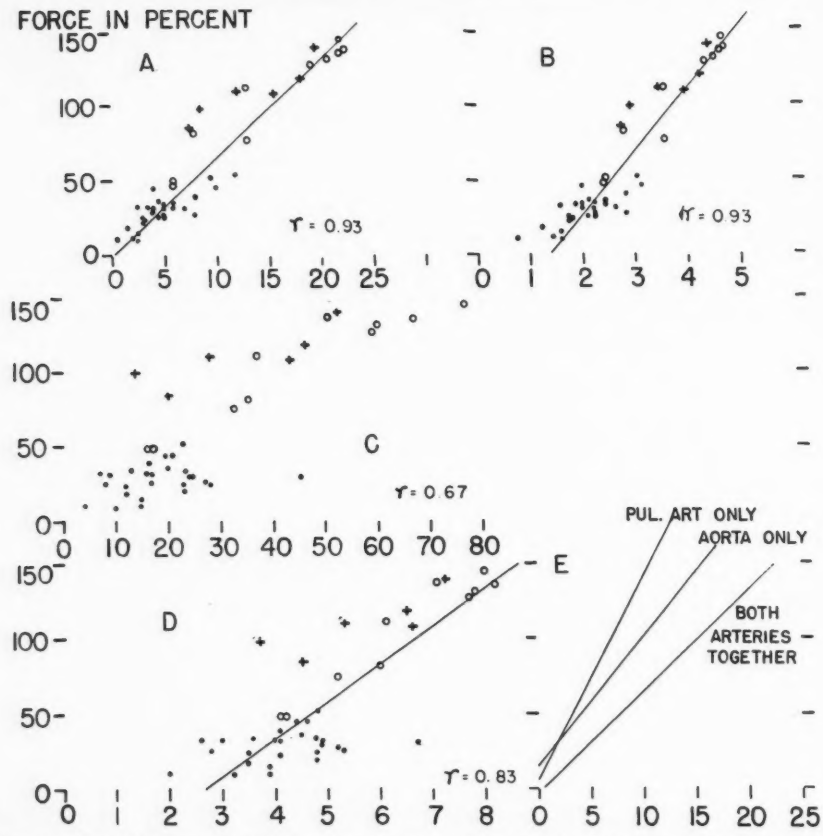

FIG. 7.—Dot Diagrams and Regressions (y on x) Showing the Relations between "Cardiac" Force and Certain Aspects of the Simultaneous Ballistocardiogram. Force is on the vertical coordinate of each diagram. The scale has been constructed as follows. Ballistocardiograms from 54 healthy men of from 20 to 39 years of age inclusive were selected. The vertical distance from the valley of I to the peak of J was measured for a typical large and a typical small complex of the respiratory cycle of each. The sum of these measurements divided by 2 gave an average value for each subject, and from them an average for the whole group was derived; it equalled 15.3 mm. The force corresponding to this value on the regression in diagram *A* above was set arbitrarily at 100 per cent. Thus, 100 represents the force which gives a ballistocardiogram of average size in healthy resting young adult males in all the dot diagrams.

A, Force and the vertical I + J distance. The scale on the horizontal coordinate is in millimeters (10 mm. = 280 Gm.).

B, Force and $\sqrt{\text{I + J distance}}$. The scale on the horizontal coordinate is in millimeters.

C, Force and the sum of the areas of the I and J waves. The scale on the horizontal coordinates is in mm. sec. × 100.

D, Force and the square root of the sum of the wave areas. The horizontal coordinate is in mm. sec. × 100.

E, Force and the vertical I + J distance. Scale as in *A*. The three regressions (y on x) were calculated from experiments in which *only the pulmonary artery* was injected, in which *only the aorta* was injected and in which *both* were injected together. The diagram shows the contribution of each side of the heart to the ballistocardiogram at any force, but when the forces are very small the estimate is inaccurate.

closer than these correlations indicate, for part of the scatter is due to errors of measuring the two curves. For estimation of these errors, both the I and J distance on the ballisto-

cardiogram and the difference between the first two points on the cardiac ejection curve were re-read, after a period of several months, and in ignorance of the first reading. The correlation between the first and second readings, the test-retest correlation, was 0.99 in each instance. These values permit us to obtain a truer value for the correlations between cardiac force and the I and J waves, a maneuver called correcting the coefficient for attenuation.[11] This raises the coefficients given in table 1 by 0.01; thus 0.93 becomes 0.94, the latter being a better indication of the true relationship.

At first glance it might appear that the superiority of the sum of the I and J vertical heights, or the square root of this distance, over the sum of the wave areas or its square root, throws doubt on the validity of Equation 3, as this suggests that the ballistocardiogram should be integrated before comparing it with force. However, we are correlating with maximal and not with total force, and maximal acceleration usually occurs in the very first instant of ejection. Successive derivatives of this part of the curve are the same in value as figure 3 shows, so that it is not necessary to integrate the ballistocardiogram in order to estimate initial force.

The validity of Equations 2 and 3 is supported by a study of the latter part of the curves. The linear depth of the K waves, correlated with the maximum calculated forces directed footward, gives a coefficient of only 0.34, which is just significant. But when compared with the corresponding maxima of the first derivative of the same forces, the correlation rises to 0.90, which is extraordinarily good and significantly better than 0.34. At the beginning of systole the situation is less complex because the force first manifesting itself escapes neutralization by other forces.

Contribution of right and left hearts to the ballistocardiogram. Regressions of the same type, correlating our estimate of force with the vertical I and J distance, have also been calculated from data secured in those experiments in which the aorta and the pulmonary artery were injected separately. The correlations are in table 1 and the regression equations in table 2, the dot diagrams of some of them being plotted in figure 7. The results permit us to ascertain the contribution of the two sides of the heart to the total impact, a problem previously considered.[2] Apparently, in normal ballistocardiograms the movement of the blood in the pulmonary artery contributes about 45 per cent of the total, that in the aorta about 68 per cent. It is to be noted that the sum of these is 113 per cent, and this suggests that some of the vectors overlap and neutralize each other when both arteries are injected together. The slight difference in the size and position of the two arches is probably enough to account for this. The contribution of blood in the pulmonary artery to the ballistocardiogram proves to be somewhat larger than that originally estimated.[2] In Experiment 4, in which the aorta and pulmonary artery were injected both separately and together, the results are consistent with those secured from the data as a whole.

TABLE 1.—*Correlation Coefficients*

From Experiments in Which:	r	Level of Significance p = 0.05
I. Both arteries were injected simultaneously		
A. Maximal force and vertical I to J distance	0.93	0.31
B. Maximal force and $\sqrt{\text{vertical I to J distance}}$	0.93	0.31
C. Maximal force and area I wave + area J wave	0.67	0.31
D. Maximal force and $\sqrt{\text{area I + area J waves}}$	0.83	0.31
E. Maximal negative (footward directed) force and vertical depth of K wave	0.34	0.31
F. Maximal negative point of the first derivative of force and the vertical depth of the K wave	0.90	0.31
II. The aorta only was injected. Maximal force and vertical I to J distance	0.79	0.33
III. The pulmonary artery only was injected. Maximal force and vertical I to J distance	0.78	0.44

Calculation of maximal cardiac force. The maximum of the heart's force which results

in the acceleration of blood in any systole can be calculated from the ballistocardiogram (the answer being given in relative terms) by equations derived from the regressions given in table 2. With a ballistocardiogram calibrated so that 280 Gm. deflected the light spot 1 cm., one would proceed as follows. If the vertical distance from the downward directed peak of I to the base line is 4 mm., and from this base line to the upward directed J peak is 8 mm., using regression A in table 2, we have

$$6.6\ (4 + 8) - 1. = 78 \text{ per cent}$$

The answer is in per cent of a standard cardiac force, the average maximum force developed by the systoles of healthy young men lying at rest. This average value for men has been arbitrarily set at 100 per cent. The average value of 49 healthy women, 20 to 39 years of age, was exactly 75 per cent of the corresponding value for men.

It must be kept in mind that this standard of force is not a normal standard, so that the result obtained does not of itself measure the normality of any given case. In all subjects the force of the beats varies with the respiratory cycle. The equations in table 2 and the calculation above give an answer not adjusted for the size of subjects; persons who are small give lower values than the standard because their small hearts beat less forcefully than do larger hearts. Also, as experience shows that the spread of the ballistocardiogram decreases with age in healthy persons,[12] older hearts beat less forcefully than younger ones. The standard deviation being 17 per cent of the mean value for men, the accuracy of the estimation is such that two-thirds of the single estimates will deviate from the true value by an amount which is less than this. For both sexes together, because of the smaller mean value, this figure is 20 per cent. If the problem before one requires greater accuracy than this, the averaging of several estimations would supply it.

The scatter of our method may appear large, and compared with the methods available to physicists and chemists it is indeed very large. But our method of estimating cardiac force compares favorably with the methods available to clinicians, for it is not inferior to the estimate of systolic pressure by the auscultatory method. Correlating the auscultatory and intra-arterial pressure measurements (Ragan and Bordley's data[13] in their figure 3), we find r = 0.90, which can be compared with r = 0.93 for our method of estimating the maximal resting cardiac force. Fisher's z test shows that the two are not significantly different.

TABLE 2.— *Equations for Estimating the Maximal Cardiac Force in Any Systole from Measurements of the Ballistocardiogram and the Scatter of the Different Methods*

Equation	Regression (y over x)	Sigma (y over x) in % of Young Adult Male Average
A	Maximal Cardiac force (in % of young men, average) = 6.6 (I + J vertical distance mm.) − 1.	16.9%
B	Maximal Cardiac force (in % of young men, average) = 40.3 $\sqrt{\text{I + J vertical distance mm.}}$ − 54.8	16.7%
C	Maximal Cardiac force (in % of young men, average) = 1.64 (area of I + area of J waves in mm. sec. × 100) − 9.3	36.2%
D	Maximal Cardiac force (in % of young men, average) = 2.34 $\sqrt{\text{area of I + area of J waves in mm. sec.} \times 100}$ − 65.7	27.3%

Normal standards. Normal standards for our estimate of cardiac force have been secured from the series of healthy persons tested in 1937–1939,[5] after the elimination of those who failed to remain healthy. Samples of about 100 persons were selected, age ranging from 20 to 39 years and the sexes being distributed almost evenly.

Since the maximal cardiac force varies from beat to beat as the respiratory cycle alters the filling of the heart, one must think of an average force for each person such as could be derived from the ballistocardiogram by measuring each cardiac complex throughout

a respiratory cycle and averaging the results. In practice, however, it suffices to select by inspection a typical representative of the smallest and another of the largest complexes and to average measurements made on these. However, a step is saved if the normal standards are made for the sum of these measurements rather than for their average; Equations *A* and *B* in Table 3 have been set up in that way. In accord with Tanner's views,[15, 16] we have employed regression equations rather than ratios and have used body surface area as a measure of the size of the subjects.

TABLE 3.—*Normal Standards for Maximum Cardiac Force in Resting Subjects*

Regression equations from data secured on 100 healthy young adults of both sexes and from 20 to 39 years of age (for obtaining the values to be expected for any subject and the scatter of healthy subjects about the value so obtained). I, J, I_2, and J_2 equal the vertical depths and altitudes of I and J waves in typical large and small complexes of the respiratory cycle. By calibration, 10 mm. deflection = 280 grams.

Equation	Regression Equations (y over x)	Standard Deviation About the Regression (y over x)	
		Absolute values	Per cent of series mean
A	$I + J + I_2 + J_2$ mm. = 23.6 (subject's surface area sq.m.) − 13.35	6.4 mm.	24%
B	$I + J + I_2 + J_2$ mm. × pulse rate per min. = 1230 (subject's surface area sq.m.) + 267	466	26%
C	I + J mm. = 7.91 (subject's surface area sq.m.) + 4.48	3.46 mm.	22%
D	$I_2 + J_2$ mm. = 4.49 (subject's surface area sq.m.) + 1.42	2.54 mm.	23%

The best type of normal standard to use can be decided only on the basis of utility; hence, several types have been calculated and others could be readily set up. Thus we wondered whether an abstract conception such as *maximal cardiac force per minute* might not have advantages over the maximal force per beat in detecting abnormality. This regression is given in table 3, but the addition of the pulse rate as a factor did not improve the scatter as we had expected. Also because abnormality of ballistic form is so often confined to the smallest complexes, and because the evidence of Brown et al.[14] has suggested that increased difference between largest and smallest complexes indicates myocardial abnormality, we have included in table 3 normal standards for both the smallest and the largest complexes of the respiratory cycle.

To determine from the ballistocardiogram whether the heart's strength is normal, one would proceed as follows. After inspection of the record, one of the smallest and one of the largest complexes are selected as typical of those found on the record as a whole, and the vertical depth of the I and the height of the J waves from the base line are measured for each. If one uses a ballistocardiograph calibrated so that 280 Gm. displaces the light spot 1 cm., the measurements in mm. are used without adjustment; if the calibration differs, the adjustment is inversely proportional. For example, if 280 Gm. displaces the light spot 2 cm., the measurements made on the record should be halved. The sum of these measurements, $I + J + I_2 + J_2$, adjusted if necessary, is used as in the following example.

If we find: in a typical small complex, I = 2 mm., J = 5 mm.; in a typical large complex, I_2 = 4 mm., J_2 = 7 mm.; and if the patient's surface area is 1.80 sq. m , then

$$Patient's\ I + J + I_2 + J_2 = 18\ mm.$$

From table 3, Equation *A*, we estimate the expected $I + J + I_2 + J_2$

$$Expected\ I + J + I_2 + J_2 = 23.6\ (1.80) - 13.35 = 29.13$$

The difference between the expected value and that found:

$$18 - 29.13 = -11.13$$

thus the deviation from the expected value is

$$\frac{-11.13}{29.13} = -38\%$$

The significance of the deviation, the probability of the case being abnormal, is obtained

by dividing the difference by the standard deviation of Equation *A*, found in table 3, thus:

$$\frac{11.13}{6.4} = 1.74$$

From this quotient, the critical ratio, the probability of abnormality can be found in any book on statistics. Conventionally, only if this ratio exceeds 2 is the result judged significantly different from the normal, but the probability thus demanded, over 97.5 in 100, is so far beyond that on which most clinical judgments are based that one wonders whether a less exacting standard would not be more useful. Certainly, if a probability of this magnitude is not attained the result should not be neglected, as statisticians would so often have us do, for the clinicians' judgment will be based on other considerations as well, and the sum of several items, each not significant if considered alone, may yield a highly significant result when considered together. If the critical ratio is over 1.30 and the sign of the deviation known, as will be the case when these normal standards are employed, the probability of abnormality is over 10 to 1, which seems sufficient for most clinical purposes.

On the other hand, if greater accuracy is required, the mean of two or more estimates can be used. The significance of the difference between this mean and the expected value is determined by dividing the standard deviation given in table 3 by the square root of the number of estimates, and dividing the difference by this quotient.

Thus, if in the patient mentioned before, we have two estimates, $I + J + I_2 + J_2 = 20$, and $I + J + I_2 + J_2 = 16$, averaging 18, then:

$$\frac{\frac{11.13}{6.4}}{\sqrt{2}} = 2.2$$

The critical ratio, now exceeding 2, meets the more rigid requirements.

It should be noted that these normal standards are not adjusted for the diminution of cardiac force which occurs with aging; whether standards with this factor included would be more useful is difficult to decide. Some elderly people have ballistocardiograms as large as those of young adults; if the normal standards are adjusted for age, these results may be found to lie outside the normal range. While the evidence is still meagre, it suggests that these subjects are actually in better health than the average for their age, that they have indeed preserved the vigor of their youth. For this reason, the age factor has not been included in the normal standards here presented. Without such a factor, the percentage of elderly persons judged abnormal will undoubtedly be large, but this information may be well worth having.[12]

In the estimation of cardiac output from the ballistocardiogram, only complexes of normal form could be employed[1]; no such limitation exists for the estimation of maximal force and any complex, no matter what its form, may be used.

Clinical significance of the result. The information about the heart provided by the new data differs from that available to clinicians before; it does not concern cardiac output, nor is it cardiac work, as this has been calculated from output. One should think of it as an estimate of the heart's strength or power, and its nature can best be made plain by an example within the experience of everyone.

Let us compare two automobiles, a large powerful car and a small, far less powerful one, and ask ourselves how we could tell them apart by their performance. Both are capable of any speed within the legal limit so that the time ordinarily required to get from place to place will not suffice as a criterion. Tests of maximum potentiality, maximum speed on the level or up steep hills, would distinguish them, but such unusual tests are conducted at a hazard. An easy way of distinguishing on the basis of their ordinary performance is to observe their acceleration from a standing start; for when the light turns from red to green, the more powerful leaves the other far behind. The product of their acceleration and mass, then, would readily establish the difference in power, and the heart's performance in accelerating the blood should similarly serve to distinguish strong hearts from weak ones.

A final example may make the new viewpoint still clearer. In figure 8 are two hypo-

thetical cardiac ejection velocity curves. In one, the velocity rises rapidly so that its maximum is attained early in systole, as is true of normal hearts. In the other, velocity rises slowly and its maximum is attained in the latter part of systole, as often occurs in weakened hearts. The tests hitherto available will not distinguish the difference between these two situations, for the cardiac output, the area under each curve, is the same in both, and cardiac work, as it is usually calculated from cardiac output, might be the same in both.

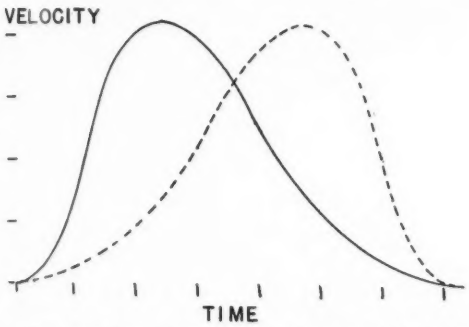

FIG. 8.—Two Hypothetical Curves of Systolic Ejection Velocity. Solid line: Here acceleration is great and maximal velocity is attained early in systole. Dotted line: Here acceleration is more gradual and maximal velocity is not attained until much later in systole. Note that the cardiac output, the area under each curve, is exactly the same in the 2 cases; hence, a difference of this type would not be detected by estimations of cardiac output per beat, or by estimations of cardiac work based on estimation of cardiac output. The ballistocardiogram easily distinguishes between the two situations. The heart accelerating the blood rapidly is beating with more force, it can save its strength and still not sacrifice its output by accelerating the blood more slowly.

Nevertheless, we know by experience that rapid lifting of a load requires more strength than lifting it slowly and, like a weakening man, the weakening heart—though unable to exert normal force—can maintain its output by lifting its load more slowly. It is this important aspect of cardiac function, the rate of lifting the load, which can be measured by the ballistocardiogram, which thus provides evidence of the strength or weakness of the heart.

However, certain reservations must still be made. The test described gives information about only one aspect of the heart's work, that employed in imparting movement to the blood. Not recorded by the ballistocardiogram is that part of the heart's force which is employed in overcoming resistance. This latter is related to the blood pressure. How the clinical estimate of blood pressure can be most profitably combined with the data obtained from the ballistocardiogram in an estimate of total strength will be a subject for further study.

The standards set up in this article enable one to test the strength exerted by the heart while the subject is at rest, and not the strength of which the heart is capable. Should tests of maximum capability be thought more valuable, their standards could be readily set up.

SUMMARY AND CONCLUSIONS

1. At necropsy, using cadavers lying on the ballistocardiograph, fluid has been injected into the aorta, the pulmonary artery, and into both together; the amount injected was optically recorded at each instant, while simultaneous ballistocardiograms were taken. By this means, the ballistocardiogram has been standardized and the accuracy of its methods tested.

2. The relationship between the "cardiac ejection curve" and the ballistocardiogram has been studied mathematically; the ballistocardiogram is closely related to the third derivative of the cardiac ejection curve. This discovery has permitted a more exact theory of the genesis of the ballistocardiogram and has considerably increased our knowledge of its relation to cardiac function.

3. The contour of the cardiac ejection curve can be reproduced by triple integration of the ballistocardiogram but the errors, magnified by the repeated integrations, proved too great to permit the quantitative estimation of cardiac output by this method.

4. While the relationship of the ballistocardiogram to the heart's output is a distant one, its relationship to the heart's force is close, and this latter has been especially studied.

5. The maximum cardiac force at any systole, calculated in our experiments as the product of maximal acceleration and an assumed mass, can be readily estimated from the spread of the ballistocardiogram, the answer being given in

relative terms. The accuracy of this method has been defined and found equal to that of estimating systolic blood pressure by the auscultatory method.

6. Normal standards for the clinical estimation of the maximal cardiac force of resting subjects are set forth. It is believed that they permit a ready estimate of the strength, or weakness, of the heart's beating in any case.

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Long-Term Dicumarol Therapy to Prevent Recurrent Coronary Artery Thrombosis

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Seventy-eight patients were given long-term dicumarol therapy after one or more attacks of myocardial infarction to see whether recurrent attacks could be warded off. Encouraging results ensued over periods up to five years. Protocols of 12 fatal cases are given, only 4 of whom had recurrent acute coronary thrombosis. Hemorrhagic complications met with are analyzed. Ambulatory treatment is shown to be feasible if patients are painstakingly followed.

FOLLOWING an attack of acute coronary thrombosis and/or myocardial infarction certain patients were selected to continue the use of dicumarol for the "long term" in the hope of preventing recurrent attacks. The premonitory signs of an acute attack are often absent and when present are frequently misinterpreted except in retrospect, and as no method of selecting the critical time to administer anticoagulants as a preventive measure is known, dicumarol must be used continuously in any attempt to forestall recurrent coronary thrombosis. The fear that coronary artery intimal hemorrhage induced by dicumarol might play a significant part in the pathogenesis of *recurrent* coronary thrombosis in patients taking dicumarol continuously has been allayed by the failure to discover any significant incidence of coronary subintimal hemorrhage at autopsy in individuals treated with anticoagulants, both in the study of 90 autopsy subjects by the American Heart Association "Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction,"[1] and in careful histologic studies* of 22 necropsy subjects, derived from 248 private patients with cardiovascular lesions of all types treated with dicumarol by one of us (E. S. N.).

Method

The Quick one-stage method of prothrombin determination was used, with a commercial rabbit-brain thromboplastin (Difco) being employed; in many of the patients the Link-Shapiro modification with the use of a commercial rabbit-lung thromboplastin (Maltine), served as a "double-check" to insure technical adequacy. We doubt that estimating prothrombin activity by the two-stage method of Warner, Brinkhaus, and Smith will prove to be a safer guide in dosage. The question of the optimal depression of prothrombin activity is not settled. Brambel and co-workers[2] have had excellent clinical results in 3,304 postoperative patients with depression of prothrombin activity to only 40 to 50 per cent, with virtually no serious hemorrhage. Our own observations, and the experience of others,[3, 4] suggests, however, that thrombo-embolization is more likely to occur if the prothrombin activity exceeds 30 per cent of normal than if it is in the 10 to 30 per cent bracket. It is less confusing to compute dosage with reference to the prothrombin time in seconds rather than percentage of prothrombin activity. Shapiro and Weiner[5] state: "It seems to us that to follow adequately the prothrombin response to 'dicumarol,' the clinician should know the normal range of the thromboplastin used and the therapeutic range he wishes to establish in terms of time. With this knowledge the calculation of percentage is superfluous; without it the percentage figure is misleading." For practical purposes we advocate using sufficient dicumarol to maintain the prothrombin time at two to two and one-half times the normal, which in our laboratory permits a range of twenty-four to thirty-eight seconds (the average normal prothrombin time with the technique used being 13.5 ± 1.5 seconds). Comparison with serial dilution curves shows that the range of twenty-four to thirty-eight seconds is equivalent to 30 to 10 per cent prothrombin activity.

After the first three weeks, prothrombin tests were made at four-day intervals, and this was gradually extended to seven-day and even ten- to fourteen-day intervals after several months in some patients. Only reasonably intelligent patients were selected and all were well informed concerning the purpose of treatment with dicumarol and the risk if directions were not followed. Urinalysis was performed at least once a month and liver function studies were made approximately every six months.

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* Dr. Philip Rezek of the Department of Pathology, Jackson Memorial Hospital, Miami, made the pathologic studies. Numerous sections of coronary arteries were studied, but examination of complete serial sections was too monumental a task to be undertaken.

Clinical description of 78 patients given dicumarol prophylactically for periods ranging from three to sixty-two months follows: Forty-four patients received dicumarol for three to twelve months, twenty-three for twelve to twenty-four months, 8 patients for twenty-four to thirty-six months, 2 for thirty-six to forty-eight months, and one for sixty-two months. There were 12 patients under 50 years of age, 34 between 50 and 60 years, and 32 between 60 and 75 years. Thirty-three patients had experienced more than one attack of coronary thrombosis. Seventeen patients were not placed on the regimen until some time after their acute attack, when, because of increasing angina or acute coronary insufficiency, dicumarol therapy was started. Five cases included in this study were the subject of a preliminary report by Nichol and Fassett;[6] of these, 2 fatal cases are described and the clinical sequel of 3 patients still living is given.

Results

In 9 patients therapy was discontinued after three to twenty-three months—in 2 because of change in residence, in four because of lack of cooperation or difficulty in obtaining prothrombin determinations, and in 3 because of hemorrhagic complications (see below). Twelve patients, or 15.3 per cent of the group, died while under treatment—in 4 death was due to recurrent attacks of coronary thrombosis; in 6 it was ascribed to either acute coronary insufficiency, congestive heart failure, or "cessation of cardiac activity" (probably ventricular fibrillation or ventricular standstill). Cerebral hemorrhage was the cause of death in 2 patients. Autopsies were performed in 8 cases, revealing fresh coronary thrombosis or infarction in 3. No mural thrombi or other complicating thrombo-embolic manifestations were found.

Analysis of Deaths

Case 1.—The patient, J. P.*, aged 52 years, a hypertensive, had three attacks of coronary thrombosis in seventeen months and was incapacitated because of coronary insufficiency for the ensuing year. Dicumarol was then given for twenty-one months with clinical improvement. The patient died in fourth attack on July 1, 1946, preceding which he probably reduced dicumarol to ineffective dosage. Autopsy showed old coronary thrombi, aneurysm of left ventricle, recent posterior wall infarction.

Case 2.—The patient, H. S., aged 65 years, was a feeble man with auriculoventricular and intraventricular block complicated occasionally by ventricular tachycardia. He began dicumarol therapy after his third attack of coronary thrombosis. Death occurred on Aug. 8, 1947, from a "stroke" after eight months of dicumarol treatment when prothrombin time was twenty-nine seconds (19 per cent PA*). Autopsy revealed a ruptured lenticulostriate artery with massive cerebral hemorrhage, myocardial scarring, old coronary thrombi, and left ventricular hypertrophy. Dicumarol probably did not initiate the apoplexy but made the hemorrhage more massive.

Case 3.—The patient, J. L., aged 53 years, had acute coronary thrombosis, but dicumarol therapy was discontinued on the tenth day because of hematuria due to hemorrhagic urethritis from an indwelling catheter, requiring transfusion. Femoral phlebothrombosis and pulmonary embolism occurred three weeks later, following which dicumarolization was successfully used for five months until May 12, 1947, when death occurred one hour after the patient experienced acute substernal pain. Prothrombin time seven days prior to death was twenty-seven seconds (20 per cent PA). Autopsy showed *old* myocardial infarction and a red thrombus (?) in the posterior descending coronary branch and left pleural adhesions. Death was attributed to acute coronary thrombosis, although microscopic studies failed to confirm thrombus formation.

Case 4.—The patient, F. B.,† aged 65 years, developed his second coronary thrombosis in April 1946, at which time dicumarol therapy was started. Intraventricular block and congestive heart failure were present. In December 1946, gross hematuria appeared when prothrombin time was twenty-eight seconds (19 per cent PA), and bleeding from hemorrhoids occurred in October 1947. Two months later when the prothrombin time was twenty-seven seconds (20 per cent PA) he developed more acute congestive heart failure with nodal tachycardia, but no electrocardiographic evidence of fresh myocardial infarction followed. Abdominal tenderness and distention developed. Right thoracentesis yielded 700 c.c. of straw-colored fluid one week prior to death, which occurred after twenty-one months of dicumarol therapy, when the prothrombin time was thirty seconds (15 per cent PA). Autopsy showed cardiac hypertrophy, left ventricular aneurysm, and the coronary arteries occluded at many points, but no fresh infarction was found. Right hemothorax, bilateral bronchiectasis, bronchopneumonia, and hypertensive arterial changes in the kidneys were found. The liver showed passive congestion and a lymphangioma containing pin-point areas of hemorrhage. Several unexplained minute perforations of the cecum gave rise to a fibrinous peritonitis.

Comment.—The hemothorax, which presumably was derived from the trauma of thoracentesis a week prior to death during dicumarol therapy, was a

* Described in preliminary report with microscopic illustrations.[6]

* PA = prothrombin activity.

† This patient lived fifteen months after the preliminary report.[6]

contributing but not a major cause of death. Congestive heart failure and peritonitis were the major causes of death. The unusual lymphangioma of the liver was an incidental finding, and although pinpoint hemorrhages were found therein, this could hardly be completely attributed to dicumarol as it is rather characteristic of this type of tumor.

Case 5.—The patient, R. E., aged 72 years, a hypertensive with previous myocardial infarction, received dicumarol therapy, in spite of chronic nephritis, because of coronary insufficiency, cerebral arteriosclerosis, congestive heart failure, and phlebothrombosis of the left leg veins. On Jan. 26, 1948, after two months of dicumarol therapy, he lost his power of speech and had clonic convulsions. Prothrombin time was thirty-six seconds (12 per cent PA) and after 300 mg. vitamin K were given intravenously during the next thirty-six hours it dropped to twenty-two seconds (35 per cent PA) without further change in spite of 160 mg. vitamin K given during the next twenty-four hours. The spinal fluid was normal. Convulsions recurred and death ensued on the fourth day. At autopsy the heart weighed 800 grams and showed marked fibrosis, and old occlusion of the left coronary artery. The cerebral vessels were markedly sclerotic with a few scattered pin-point hemorrhages in the internal capsule and pons. Bronchopneumonia, hepatic congestion, and renal hypertensive arterial changes were noted. The pancreas was fibrotic and was the seat of a small hemorrhage.

Comment.—The relationship of the pancreatic apoplexy to the terminal clinical state is difficult to evaluate, and it is questionable whether dicumarol induced it. The petechial hemorrhages in the internal capsule and pons, considered to be the cause of death, were possibly due to dicumarol.

Case 6.—The patient, M.S., aged 60 years, a hypertensive, was continued on dicumarol therapy following his third coronary thrombosis and was moderately active in spite of congestive failure. His anginal pain lessened, but after five months, on Sept. 22, 1948, he died suddenly. The prothrombin time nine days earlier was twenty-six seconds (20 per cent PA) and he had continued his weekly dicumarol dosage of 425 milligrams. Autopsy disclosed petechiae, coronary sclerosis, old myocardial infarction, left ventricular aneurysm, mottled subendocardial hemorrhages on the posterior aspect of the septum, but no fresh coronary occlusion or myocardial infarction. Microscopic sections of the mottled areas of the septum disclosed the same degree of hemorrhage that is often found following fatal acute coronary insufficiency which presumably was the cause of death.

Case 7.—The patient, L. H., aged 55 years, had an acute anterior myocardial infarction on Oct. 7, 1946, when dicumarol therapy was started, his requirement being 150 mg. daily. Prothrombin activity was 29 per cent two days before recurrent fatal coronary thrombosis on March 16, 1947. Autopsy disclosed coronary sclerosis, old thrombosis of left anterior descending and right coronary arteries, and recent thrombosis of the circumflex artery.

Case 8.—The patient, A. H., aged 65 years, had decompensated hypertensive heart disease and coronary insufficiency. He received 50 mg. of dicumarol daily for eight months. He died suddenly on Oct. 19, 1948, without a recent prothrombin determination. Autopsy was restricted to the heart which showed no fresh coronary thrombosis, only a severe grade of coronary sclerosis and myocardial fibrosis.

Case 9.—The patient, J. R., aged 62 years, was started on dicumarol therapy after an acute posterior myocardial infarction on Jan. 29, 1947, his requirement being 50 mg. daily. Prothrombin activity was 15 per cent six days before a *recurrence* of coronary thrombosis. Three weeks later he died suddenly after taking dicumarol for three months. No autopsy was performed. Presumably death was due to functional cessation of cardiac activity.

Case 10.—The patient, J. W., aged 58 years, a hypertensive, was started on dicumarol therapy on Aug. 28, 1946, because of persistent pain following myocardial infarction. He improved but six months later developed microscopic hematuria and purpura when the prothrombin time was sixty seconds (6 per cent PA). Vitamin K was given intravenously and dicumarol omitted for one week, when he developed acute coronary insufficiency with subendocardial infarction during a period of normal prothrombin activity. Heparin and dicumarol therapy produced rapid improvement. In October 1947, he developed a transitory "cerebral vascular crisis" which recurred three months later. General muscular cramps developed in the spring of 1948. On Aug. 1, 1948, while taking his customary dicumarol dose of 900 mg. weekly, with the prothrombin time at twenty-three seconds (25 per cent PA), he developed somnolence and weakness and a few days later was unable to talk coherently for some days. On Dec. 22, 1948, when the prothrombin time was seventeen seconds (50 per cent PA), he became disoriented and could not move without aid, and had tremors and ankle clonus. Rigidity of the extremities and coma appeared before he expired on Dec. 30, 1948. No autopsy was performed.

Comment.—As this patient had been partaking of Westsal liberally, in retrospect we believe lithium poisoning contributed to his death, although cerebral vascular disease was marked.

Case 11.—B. S., aged 60 years, had coronary thrombosis in 1943 followed by left ventricular hypertrophy, congestive failure, and angina pectoris. On Nov. 8, 1947, dicumarol therapy was started because of premonitory signs of myocardial infarction. The patient improved and had only occasional anginal pain until he died suddenly after five months of dicumarol therapy. The prothrombin time four days prior to death was twenty-three seconds (25 per cent PA). No autopsy was performed.

Comment.—The degree of congestive heart failure

at death was not marked so presumably death resulted from cessation of cardiac activity.

Case 12.—The patient, A. P., aged 65 years, a hypertensive, gave a history of cerebrovascular accident seven years previously. Dicumarol was started, because of angina pectoris and left ventricle failure, on Aug. 18, 1948, one month after he developed acute coronary thrombosis. His anginal pain subsided but mild left ventricle failure persisted. He died suddenly after approximately three months of dicumarol therapy. The prothrombin time five days before death was twenty-one seconds (38 per cent PA). No autopsy was performed. Death was attributed to functional cessation of cardiac activity.

In seven of eight autopsied patients who had used dicumarol for two to twenty-three months, no toxic changes were found in the liver or kidneys attributable to dicumarol except for the possibility that the microscopic hemorrhage in the hepatic hemangioma in patient 4 might have been due to the dicumarol, although this is unlikely. No evidence of liver or renal injury after one or more years of dicumarol therapy has developed in the living patients.

Clinical Sequel of Living Patients

In the 57 patients remaining on dicumarol, anginal pain has been minimal or absent in nearly all, in spite of their being moderately active in business or home. The willingness of patients to adhere to the regimen faithfully reflects substantial subjective improvement hardly fully attributable to the psychotherapeutic effect of taking dicumarol. Four of the living patients have experienced episodes of acute coronary insufficiency with possible subendocardial infarction followed by recovery without thrombo-embolic complications. The clinical features of one exceptional case, occurring in an elderly woman who developed a third recurrent acute myocardial infarction while dicumarol was in force, follow:

Patient Mrs. J. R., aged 63 years, had survived an attack of myocardial infarction thirteen years previous to development of premonitory signs of coronary thrombosis on Sept. 2, 1948. She was given heparin and dicumarol but continued to have cardiac pain with occasional nausea and vomiting. When the prothrombin time was forty-six seconds (9 per cent PA), fifteen days after onset, following severe pain, the electrocardiogram showed evidence of anterior wall infarction. Complete relief of her pain, much of which was provoked by the gastrointestinal tract, was not obtained. By the sixth week she was able to be slightly ambulant. The prothrombin time was maintained between twenty and thirty-five seconds (40 to 10 per cent PA). On Jan. 19, 1949, she had severe substernal pain when the prothrombin time was thirty seconds (18 per cent PA). The electrocardiogram showed changes indicative of acute anterolateral myocardial infarction. Congestive heart failure and various ectopic rhythms appeared, and heart failure persists four months later, but the patient is able to be ambulant at home with only mild anginal pain.

This patient developed acute myocardial infarction while on dicumarol fifteen days after onset of premonitory signs, and four months later, while on supposedly adequate dicumarol therapy, a frank anterolateral infarction developed. Obviously dicumarolization did not forestall a recurrent attack, and her case demonstrates that the regimen even when carefully followed may fail to prevent coronary thrombosis.

Eleven patients have followed the regimen two years or longer without recurrence although six had multiple previous attacks. The clinical sequel of 3 surviving cases described in the preliminary report[6] follows:

Patient W. A. S., a 53 year old hypertensive man, had anterior myocardial infarction in October 1945, with recurrence five months later. Dicumarol has been used ever since, a matter of three years. He has remained relatively free of anginal pain, and is able to work. His dicumarol requirement remains remarkably constant at 350 mg. weekly.

Patient W. T. M., a 57 year old bookkeeper, developed hypertension and left hemiplegia in 1939. Attacks of coronary thrombosis occurred in 1942 and 1945. On May 1, 1946, he had a third myocardial infarction so dicumarol therapy was initiated. In January 1947, when prothrombin time increased to fifty-nine seconds (6 per cent PA), he developed gross hematuria with renal colic but no evidence of renal calculus was found. Dicumarol was omitted temporarily and vitamin K was given with reduction in prothrombin time the following day to thirty-one seconds (18 per cent PA). Since then he has done well except for emotional instability, and is employed. He required 700 mg. or more dicumarol weekly for twenty-nine months, but in the past eight months his requirement has been nearer 600 mg. weekly, probably owing to an increase in his consumption of alcoholic beverages (figure 1).

Patient J. R. T., aged 54 years, had his first attack

of coronary thrombosis with posterior wall myocardial infarction in January 1943. In June 1943, he had a second severe attack with anterior infarction and was given dicumarol. In February 1944, he developed a third attack, ushered in by intractable pain. Dicumarol therapy was started again and was continued to see if additional attacks could be warded off. In December 1945, gross hematuria with renal colic appeared when the prothrombin time was thirty-six seconds (12 per cent PA) but no evidence of renal calculus was found. Gross hematuria has never recurred, but in November 1946, when the prothrombin time was thirty-five seconds (15 per cent PA), he developed hematemesis and tarry stools due to a bleeding duodenal ulcer which had been first diagnosed in 1942. The bleeding was soon controlled with vitamin K and 1000 c.c. whole blood, the prothrombin time dropping in twenty-four hours to twenty-two seconds (30 per cent PA) and in

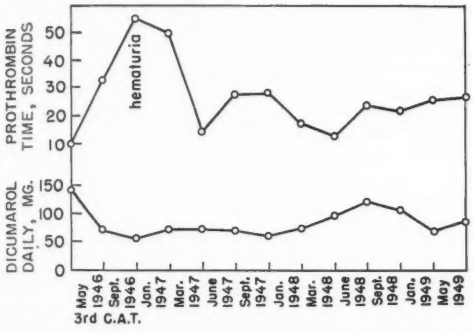

FIG. 1.—Graph of dicumarol dosage and prothrombin time of W.Mc.G. from May 1946 to May 1949. (C.A.T. = coronary thrombosis.)

forty-eight hours to sixteen seconds (80 per cent PA). Dicumarol therapy was omitted for five weeks, but was resumed because of an increase in anginal pain, and has not been interrupted again except for dental extractions. In 1947, recurrent upper respiratory infections and bronchitis appeared and pulmonary emphysema developed with reduction in vital capacity. No left ventricular failure has developed although the heart is moderately enlarged with suggestive signs of ventricular aneurysm. The patient lost weight owing to poor appetite and unsatisfactory dentures, and the pulmonary symptoms remained troublesome but improved when he took a holiday trip to Nova Scotia last summer. His dicumarol requirement was remarkably constant (700 to 800 mg. weekly for four years) until the dietary change occurred as described under "Variable Dicumarol Requirement"; since then he has required only 550 to 600 mg. weekly. He was free of any significant anginal pain until January 1949, when after overexertion, business worries, and excessive use of tobacco, he developed moderate substernal pain not associated with additional electrocardiographic changes. His feeling of well-being deteriorated somewhat but has improved again during the past four months. The probability is strong that the use of dicumarol has forestalled additional attacks of coronary thrombosis, since the patient experienced three attacks in thirteen months

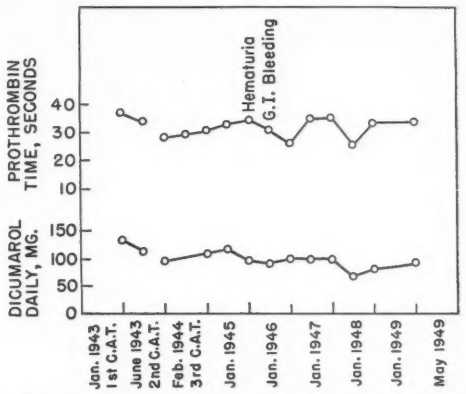

FIG. 2.—Dicumarol dosage and prothrombin time of J.R.T. from February 1944 to May 1949. (C.A.T. = coronary thrombosis.) Because of the long duration of the data, daily variations cannot be demonstrated.

TABLE I.—*Sites and Incidence of Hemorrhage in Seventy-Eight Long-Term Patients*

Minor Hemorrhage		Major Hemorrhage*	
Microscopic hematuria	3	Gross hematuria	8
Purpuric manifestations	10	Upper G. I. tract	2
Hemorrhoids	5	Hemothorax	1
Epistaxis	3	Cerebral gross	1
Episcleral	2	Cerebral pin-point	1
Buccal	1	Hematoma (injury)	1
Lymphangioma of liver	1	Subendocardial	1
Transient blood-tinged sputum	2	Pancreas	1

*Major hemorrhage occurred in sixteen sites in 13 patients.

prior to initiating the dicumarol regime over five years ago. (Fig. 2).

Complications

Hemorrhagic manifestations occurred in 28 patients (35.8 per cent), in thirteen (16.6 per cent) of whom hemorrhage was of major type (table 1). Hemorrhage occurred in some patients in more than one site and on more than

one occasion. It is to be expected that patients taking dicumarol for months or years should experience more episodes of hemorrhage than patients taking dicumarol for a few weeks only. The two fatal hemorrhages encountered have been described above (in Patients H. S. and R. E.). One occurred in a 63-year-old man who had three attacks of coronary artery thrombosis and died after eight months of dicumarol therapy with massive cerebral hemorrhage due to rupture of the right lenticulostriate artery. The other took place in a 72 year old hypertensive man with coronary artery disease and congestive heart failure, who, after two months of dicumarol therapy, died in coma and convulsions due to petechial hemorrhages in the internal capsule and pons.

In only 3 patients was it necessary to abandon the dicumarol regime because of hemorrhage: In one of these patients repeated hematuria associated with urologic disease occurred after five months of therapy; in another hemorrhage into the shoulder joint followed automobile injury after twenty-three months of therapy; in the third, massive, silent gastrointestinal hemorrhage occurred after thirteen months of therapy. This last patient was a Greek man with an alcoholic history. Gastrointestinal x-ray studies and liver function studies showed no abnormality when his prothrombin time reached sixty seconds (6 per cent PA), following an increase in his weekly dosage from 400 mg. to 500 mg. during a period of increased consumption of alcoholic beverages. An episode of hematuria had occurred three months previously in this patient when the prothrombin time was thirty-five seconds (15 per cent PA), yet no hematuria developed at the time of the gastrointestinal hemorrhage in spite of the prothrombin activity being only 6 per cent, which shows the unpredictability of dicumarol-induced bleeding.

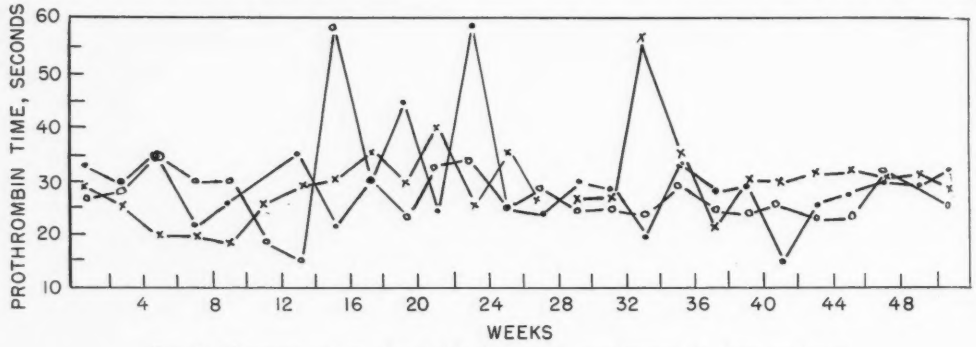

FIG. 3.—Demonstration of variable dicumarol requirement in three patients.

Long-Term Dicumarol Regimen for Fifty-two Weeks to Prevent C.A.T. (ADD = Average daily dose; AWD = Average weekly dose)

H. P. — .—.	J. S. °–°	R. D. x—x
Wh. F. — 78 yr.	Wh. M. — 51 yr.	Wh. 7 . — 52 yr.
Wgt. — 144	Wgt. — 170	Wgt. — 125
B. P. — 150/84	B. P. — 120/80	B. P. — 180/110
Dicumarol	*Dicumarol*	*Dicumarol*
ADD — 30.8 mg.	ADD — 70.7 mg.	ADD — 172 mg.
AWD — 222.5 mg.	AWD — 493.6 mg.	AWD — 935 mg.

Hemorrhagic episodes are not always well correlated with the prothrombin activity. Bleeding may occur in some patients when the prothrombin activity is only moderately reduced, and on other occasions in the same patient bleeding might not occur with considerably less prothrombin activity. Adequate amounts of synthetic vitamin K given intravenously controlled the bleeding and lowered the prothrombin time, except in 2 patients requiring transfusions. The risk of hemorrhage in anticoagulant therapy, and the obligation

of the clinician to make sure that the laboratory understands the technical pitfalls of prothrombin determinations, have been stressed repeatedly in the literature.

Variable Dicumarol Requirement

Although it has been known since earliest clinical use of dicumarol that the dosage required for producing effective hypoprothrombinemia is variable, it is not so well known that in long-term dicumarol therapy marked disparity in the weekly requirement of dicumarol by different patients may occur, as recently emphasized by Foley and Wright[7] and by Olwin.[8]

Figure 3 illustrates this variability. Of 3 patients receiving dicumarol for fifty-two weeks, one required approximately 225 mg. per week, another 500 mg. per week, and a third 950 mg. per week, to maintain the prothrombin concentration between 30 and 10 per cent of normal (twenty-four to thirty-eight seconds). Even more important is the sudden change in a patient's tolerance that may occur after many months of dicumarol therapy. This is shown also in figure 3 by the excessive peak of prothrombin time of fifty-five to sixty seconds which occurred once in the course of the year in each patient while on usual dosage. A more striking example of change in tolerance is Patient J. R. T., described above and illustrated in figure 2, who has taken dicumarol for sixty-two months, and whose usual weekly requirements were 700 to 800 milligrams. On returning from a summer trip in 1948 the prothrombin time had increased to fifty-five seconds (8 per cent PA) on his usual dosage instead of the customary twenty-five to forty seconds (22 to 10 per cent PA). Inquiry revealed that instead of drinking milk freely, as was his custom because of duodenal ulcer, he had been imbibing ale moderately, thereby apparently changing his tolerance for dicumarol. A similar relationship between dietary content of protein or alcoholoic beverages and dicumarol requirement has been commented on by Foley and Wright.[7]

Discussion

The continuous use of dicumarol over a period of years to prevent recurrent coronary thrombosis has been shown to be feasible and relatively safe. No conclusions as to the efficacy of the regime can be drawn from this small uncontrolled series. We believe a long-range cooperative study of a large group of cases should be undertaken in order to properly evaluate the effect of the regimen, even though the establishment of adequate controls would be admittedly difficult. Such a study would require the cooperation of many clinicians in private practice.

It must be borne in mind that sudden death may occur several days after the final prothrombin determination, and hypoprothrombinemia may have developed. If no autopsy is obtained, therefore, coronary artery subintimal hemorrhage, or hemorrhage in the myocardium or brain, may escape detection since clinical signs might not be present long enough for them to be recognized as causes of death. This consideration applies to the 4 patients described above who died and upon whom autopsies were not performed. It is, however, well recognized that sudden death occurs not infrequently in persons with coronary artery disease without the presence of demonstrable acute lesion. In either case the mechanism of the sudden cessation of cardiac activity is probably ventricular standstill or ventricular fibrillation.

The distinct reduction in anginal pain experienced by most of the dicumarolized group calls forth speculation as to the possible mechanism inducing such striking improvement. The probability of increased coronary blood flow due to lessened blood viscosity has been mentioned.[6] However, if the claims of Gilbert and co-workers[9] are borne out and dicumarol proves to have a strong dilating effect on the coronary arteries, this would readily explain the decrease in anginal pain. We have noted no significant reduction in bood pressure during long-term therapy in any patient, which throws doubt on the vasodilation action of the drug. In evaluating any reduction in anginal pain, it is of course necessary to consider the factor of psychotherapy. We are aware also that following myocardial infarction some patients seem to have less pain than prior to the acute episode for no well-established reason.

SUMMARY

Since 1944 dicumarol therapy has been continued indefinitely following an attack of acute coronary thrombosis and/or myocardial infarction in 78 patients in the hope of preventing recurrent attacks.

Twelve patients died, but of these only 4 had recurrent coronary thrombosis (8 autopsy studies). Nine patients discontinued therapy. Fifty-seven patients remaining on the regimen are active and doing well with little anginal complaint, and in 10 of these two or three years have passed without an attack, and in one noteworthy patient, who had three previous myocardial infarctions, over five years have passed since the last recurrence. Four of the living patients have experienced episodes of acute coronary insufficiency with possible subendocardial infarction followed by recovery without thrombo-embolic complications. One elderly patient still alive developed a recurrent myocardial infarction while dicumarolized.

Major hemorrhagic episodes occurred in thirteen patients resulting in two fatalities (only one of which could fairly be attributed to the use of dicumarol) and abandonment of the regimen in 3 other patients; the remainder resumed dicumarol treatment satisfactorily. No toxic effect on the kidneys or liver was found in 7 autopsy subjects who had received dicumarol two to twenty-three months, nor has clinical evidence of such toxicity been found in the living patients. The variability in dicumarol requirement from year to year in a few patients has been illustrated.

No conclusions are drawn from this study but actual reduction of frequency of recurrent attacks may eventually be proved. A cooperative five-year study by clinicians in private practice would reveal whether or not the long-term use of an anticoagulant justifies the trouble and risk involved.

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Hypothyroidism Produced by Radioactive Iodine (I^{131}) in the Treatment of Euthyroid Patients with Angina Pectoris and Congestive Heart Failure

Early Results in Various Types of Cardiovascular Diseases and Associated Pathologic States

By Herrman L. Blumgart, M.D., A. Stone Freedberg, M.D., and George S. Kurland, M.D.

Hypothyroidism, induced by I^{131} to lessen the work of the heart, is proposed as a means of treating certain patients with angina pectoris and congestive failure who are refractory to the standard medical measures. Eighteen such patients have been treated. The period of follow-up averages thirteen months. Eight of the 13 patients with angina pectoris and 3 of 5 patients with congestive failure showed worthwhile improvement. In 6 of the 18 patients, the improvement was striking. Tentative criteria for the selection of patients, their pre- and post-treatment management, and detailed descriptions of the results are presented.

PREVIOUS STUDIES which showed that the work of the heart is lessened in myxedema led to the employment of total thyroidectomy,[1, 2] and more recently, antithyroid drugs,[3-10] to induce hypothyroidism in patients with intractable angina pectoris and/or congestive heart failure. Concomitant clinical improvement has been witnessed, but with each method certain disadvantages have been apparent.[2, 5] The availability of radioactive iodine (I^{131}) led us to investigate its possible use for this purpose.[11]

This communication is a report of the therapeutic results of hypothyroidism induced by I^{131} in 18 euthyroid patients with advanced angina pectoris or congestive heart failure. Each patient was selected, for reasons to be detailed, from the relatively small group of cardiac cripples who remained seriously disabled and in great discomfort despite all medical measures including regulation of their activity, assistance in their emotional problems and medicinal treatment.

From the Medical Service and Medical Research Department of the Yamins Research Laboratories of the Beth Israel Hospital, Boston, Mass., and the Department of Medicine, Harvard University Medical School, Boston, Mass.

This work was carried out under a contract between the Office of Naval Research, the Atomic Energy Commission and the President and Fellows of Harvard College. This investigation was also aided by funds of the Patrons of Research, Beth Israel Hospital, Boston, Mass.

This paper was read in abstract at the annual meeting of the Association of American Physicians, May 2, 1949.

Plan of Investigation

The first problem was to learn whether persistent hypothyroidism could be induced safely by one or more doses of I^{131}. It is well known that thyrotoxicosis can be controlled by I^{131} with a reduction of the basal metabolic rate to normal. Three to eight millicuries are commonly used. The avidity of the normal thyroid gland for I^{131} is much less, however; the uptake is usually 20–50 per cent of the administered dose, as indicated by urinary excretion, and averages 30 per cent as measured by external counting.[12] Before the therapeutic studies of the present communication were undertaken, observations were made with gradually increasing doses in euthyroid patients in terminal state due to hemiplegia or other conditions such as carcinoma. The results of these studies indicated that persistent hypothyroidism could be induced by one or more appropriate doses without any toxic effects.[13, 14]

Since November 1947 we have induced persistent hypothyroidism in the 18 consecutive cardiac patients of the present report in whom the duration of the follow-up is sufficient for clinical evaluation of the therapeutic results.

Methods of Study

The clinical appraisal of the post-treatment as well as of the pretreatment condition of each patient was carried out independently by several observers. We also have evaluated the pretreatment as well as the post-treatment condition of our patients by as

many objective criteria as possible. Detailed clinical and laboratory studies were performed before, and at frequent intervals after treatment. With a few minor exceptions, the treatment of cardiac disease in each patient was the same after treatment as before treatment.

Routine examinations of the blood and urine, electrocardiograms and roentgenograms of the chest taken at a distance of 7 feet were performed before treatment and at frequent intervals after treatment. Blood for cholesterol measurements was drawn from the antecubital vein with minimal stasis after a fast of fourteen hours or more. Measurements of serum cholesterol were made in duplicate by the method of Myers and Wardell,[15] using the apparatus for continuous extraction described by Ling.[16] The averages of the duplicate determinations, which checked within 5 per cent, have been reported. Where the clinical state of the patient indicated, special studies of the blood were performed. These included nonprotein nitrogen, glucose, total protein, calcium, corrected sedimentation rate, and prothrombin time.

The basal metabolic rate, the vital capacity of the lungs and its subdivisions were measured with a Collins Benedict-Roth apparatus. Patients with orthopnea were allowed to lie in a semirecumbent position. On each occasion, measurements were made in duplicate or triplicate and were repeated before treatment until it was evident that the patient had attained the basal state. The Dubois normal standards as modified by Boothby and Sandiford were used.[17]

The venous pressure was measured by the direct method of Moritz and Tabora.[18] When possible, the readings were obtained with the patient recumbent, the right auricle being assumed to be 5 cm. below the level of the fourth costochondral junction. When orthopneic, the patient was allowed to sit up at an angle of 45 degrees, the right auricle then being assumed to be 2.5 cm. below the fourth costochondral junction.

The arm to tongue circulation time was performed with sodium dehydrocholate (Decholin) according to the methods of Winternitz, Deutsch and Brüll[19] and Gargill.[20]

Each patient received a tracer dose of I^{131} before treatment. Quantitation of the uptake in the thyroid gland following tracer and therapeutic doses was made by a four-tube method previously described.[12] The seventy-two-hour urinary excretion of I^{131} was determined by a modification of this method[21] and by the method described by Marinelli and Hill[22] and by one of us.[23] We are indebted to Dr. Douglas J. Riggs for determination of the serum protein-bound iodine in some cases.

Many of our patients with angina pectoris were too ill to be subjected to an exercise tolerance test. When the hazard was not considered significant and when the patient could undertake the necessary effort, exercise tolerance tests as described by Riseman and Stern[24] were performed before and after treatment.

Dosage, Retention and Side Effects of I^{131}

Each patient has received orally a total of 25.5 to 150 millicuries (table 1), carrier free, in single or divided doses, of which a total of 7.3 to 39 millicuries has been retained in the body during the following seventy-two hours. The largest single dose has been 56 millicuries. The average total dose has been 54.4 millicuries; the average retention, 17.9 millicuries. The patients have experienced no serious toxic symptoms; in approximately two-thirds of the patients, transitory thyroiditis characterized by slight to moderate pain and tenderness over the thyroid with pain on swallowing has been present one to fourteen days following the initial therapeutic dose. In only one instance (Case 1) was a subsequent therapeutic dose attended by clinical thyroiditis. Thus, transitory thyroiditis occurred twelve times after thirty-one therapeutic doses given to the 18 patients. It was mild seven times, moderate four times and severe once. In 7 of the 18 patients, clinical thyroiditis did not occur. Radiation sickness has not been observed. Repeated examinations of the blood and urine revealed no toxic effects.

Clinical Description of the Eighteen Patients and Results

The course of angina pectoris and congestive failure is often irregular and characterized by periods of unexpected exacerbation and remission. We have, therefore, selected only patients who, despite marked restriction of activities for many months or years, showed evidence of continued incapacity after having received all standard forms of therapy and in whom remissions of the disease were absent or who continued to suffer signs and symptoms even during periods of slight remission.

The patients with angina pectoris (table 2) suffered characteristic attacks on effort or emotion and continued to have several or many attacks a day on slight exertion such as walking short distances, bending to tie shoe laces or walking one flight of stairs; many were awakened from sleep nightly or several times a week, and had attacks after eating; several had attacks of cardiac asthma. None of the patients had been able to carry on gainful occupation except Case 7, doing light work a few hours a day, and Case 11, as an upholsterer, several hours a day. The severity of cardiac involve-

TABLE 1.—*The Dose, Urinary Excretion, Retention, and Side Effects of I^{131} Administered to Eighteen Euthyroid Cardiac Subjects*

Case	I^{131} Administered (mc.)	72-Hour Urinary Excretion (%)	Amount Retained in Body (mc.)	Side Effects*	
				Thyroiditis†	Transitory Thyrotoxicosis
1. J. L.	29	64	10.3	+	None
	43	96	1.7	0	None
	39	83	4.9	0	None
	39	97	1.2	+	None
Total	150		18.1		
2. R. A.	24	62	9.0	0	None
	27	87	3.6	0	None
	39	92	3.1	0	None
Total	90		15.7		
3. J. K.	42.5	45	23.5	+++	Probable
4. H. R.	25.5	Not feasible		++	None
5. M. G.	42.5	58	17.8	++	Yes
	25.5	82	4.6	0	None
Total	68.0		22.4		
6. S. F.	42.5	44	23.8	+	None
7. B. S.	25.5	80	5.1	+	None
	27.0	92	2.2	0	None
Total	52.5		7.3		
8. M. H.	39	70	11.7	0	None
	34	72	9.5	0	None
Total	73		21.2		
9. M. C.	15.5	64	5.4	+	None
	24.0	88	2.9	0	None
	32.0		1.6	0	None
Total	71.5		9.9		
10. R. S.	30.5	70	9.2	0	None
11. H. Y.	25.5	Not feasible	—	++	None
12. J. E.	25.5	Not feasible	—	++	None
13. M. S.	42.5	71	12.2	+	None
	56.0	71	16.2	0	None
Total	98.5		28.4		

TABLE 1.—*Continued*

Case	I^{131} Administered (mc.)	72-Hour Urinary Excretion (%)	Amount Retained in Body (mc.)	Side Effects*	
				Thyroiditis†	Transitory Thyrotoxicosis
14. R. F.	25.5	17	21.2	0	None
15. M. G.	27.0	28	19.5	0	None
	30.5	35	19.5	0	None
Total	57.5		39.0		
16. E. M.	8.5	71	2.5	0	None
	24.0	62	9.0	0	None
Total	32.5		11.5		
17. E. D.	27	43	15.7	0	None
18. N. A.	39	48	20.4	+	None

* No toxic effects on the blood or kidney, and no radiation sickness was observed in any case.
† +++ severe; ++ moderate; + mild, tenderness on palpation but no symptoms; 0 none

ment was reflected by the fact that twelve attacks of acute myocardial infarction had occurred in the 13 patients with angina pectoris. The etiologic basis for angina pectoris in all patients was arteriosclerotic heart disease; in 5, arterial hypertension was present. Eleven were men, 2 were women. The ages ranged from 38 to 72 years; the average was 57 years. The duration of angina pectoris prior to treatment was 1–18 years and averaged 5 years. The period of observation following I^{131} therapy was seven to nineteen months and averaged twelve months.

The 5 patients with congestive failure (table 3) had all been treated by prolonged bedrest and regularly showed evidence of congestive failure on getting out of bed. Three of the patients had rheumatic heart disease; the other 2, arterial hypertension and arteriosclerotic heart disease. The ages of the patients ranged from 43 to 59 years. The duration of decompensation varied from $1\frac{1}{2}$ to 17 years and averaged 7.3 years. The condition in each case was such that definite improvement could be confidently attributed to the hypothyroidism induced by I^{131}.

In some of the patients of this series, the probability of achieving a worthwhile result was admittedly small. Thus, Patient 5 had already suffered two attacks of acute myocardial infarction and several other episodes of prolonged excruciating pain but without progressive characteristic electrocardiographic changes. Similarly, Patient 18 had shown a rapidly progressive course of congestive failure with multiple embolic episodes. In all patients included in this report, reliable information regarding the characteristics and severity of the clinical course was available. Some patients had been observed for years in the cardiac clinic of the Beth Israel Hospital and on the wards; others were referred by highly competent physicians who placed their records at our disposal. Each patient was appraised independently by several of us before a decision was reached; in many instances, our appraisal was based on observation and study of the patient, including exercise tolerance and other tests, over a period of weeks or many months before radioactive iodine therapy was instituted.

No patient was chosen whose prognosis for life was good. In each instance the procedure was explained to the patient with a full account of its experimental status and the necessity for frequent follow-up studies. In some patients the treatment was inaugurated while they were still

hospitalized; in others, all studies were carried out with the patients on an ambulatory basis.

No patient showed positive evidence of hyper- or hypothyroidism before treatment. In addition to the clinical criteria, the following indices revealed normal thyroid function: the basal metabolic rate, serum cholesterol, and, in some instances, the serum protein-bound iodine. Tracer doses of I^{131} were administered and in all cases the percentage of urinary excretion was that observed with normal thyroid function. In patients with congestive failure, the urinary excretion is lower than that observed in edema-free individuals. Direct measurements of the thyroid uptake in patients with congestive failure have revealed uptakes in the euthyroid range.

The patients selected had diverse types of cardiovascular disease i.e., arteriosclerotic heart disease with congestive failure, arteriosclerotic heart disease with angina pectoris, arteriosclerotic heart disease with hypertension and paroxysmal dyspnea, rheumatic valvular heart disease with normal rhythm or with auricular fibrillation.

To obtain patients who met these requirements, only certain patients were selected from among the larger group with intractable heart disease. Some rejected patients failed to give sufficient objective confirmation of their incapacity when carefully studied; others were afflicted with associated diseases (such as bronchiectasis with advanced pulmonary emphysema, renal disease, cirrhosis of the liver, cerebral arteriosclerosis, active rheumatic fever, subacute bacterial endocarditis) which would render evaluation of the therapeutic result difficult. In others, the anticipated duration of life of weeks or a few months was insufficient to permit the induction of hypothyroidism which similarly requires weeks or months.

Case Histories with Comment

Case 1.—Angina pectoris one year, increasing in frequency and intensity; patient almost completely incapacitated. Coronary arteriosclerosis; old myocardial infarction. Four doses of I^{131}, totaling 150 mc., with temporary hypothyroidism and clinical improvement after each of the first three doses; persistent myxedema and disappearance of angina after fourth dose. Myxedema controlled by 30 mg. thyroid daily. Practically complete disappearance of all symptoms. Patient feeling well past seven months and gainfully employed. Striking therapeutic result.

Pretreatment History. J. L., a 41 year old man, B.I.H. #69433, referred through the courtesy of Dr. J. E. F. Riseman, received 29 mc. I^{131} on April 27, 1948. One year prior to I^{131} therapy, attacks of substernal pressure on exertion and emotion were first noted. He was hospitalized for eight months before treatment because of "clawing, tearing" substernal pain with momentary loss of consciousness, due to probable acute myocardial infarction. The anginal attacks increased in severity and frequency, lasted from one to ten minutes and were relieved by nitroglycerine. He had been unable to work for the previous nine months and had been restricted largely to the house because walking even a hundred feet precipitated an attack. He was awakened by anginal attacks, often suffering three or four episodes nightly. He noted increasing dyspnea and was uncomfortable unless he used two pillows. In the month prior to I^{131} therapy, he had used over 500 tablets of nitroglycerine. During his illness, he had received the following treatment: theobromine sodium acetate, potassium iodide, sedatives, quinidine, atropine; nitroglycerine alone was of slight help. There was no history of arterial hypertension or of rheumatic or syphilitic infection.

Pretreatment Physical Examination. Physical examination revealed entirely normal findings. The heart was of normal size and contour. The first sound was split. The sounds were of good quality and there was a Grade I apical systolic murmur. The blood pressure was 110/80.

Pretreatment Laboratory Examinations. (See table 2.) The urine and blood were normal. On x-ray examination, the heart was normal in size and shape. The electrocardiogram was consistent with an old posterior infarct. The administration of 150 microcuries I^{131} was followed by a three-day urinary excretion of 45 per cent (euthyroid range).

Post-treatment Course. On April 27, 1948 he received 29 mc. I^{131}; three additional doses of 43, 39 and 39 mc. were administered on July 23, August 13 and November 22, 1948, respectively (table 1). Five weeks after the first dose of I^{131}, definite clinical improvement was noted with disappearance of all but a few attacks of angina pectoris. The serum cholesterol level had risen and clinical signs consistent with hypothroidism were present. During the next few weeks, anginal episodes recurred to the pretreatment severity and frequency. The hypothyroid state was transient. Five weeks after the third dose, the serum cholesterol values rose, and the basal metabolic rate became lower. The patient experi-

TABLE 2.—*Summary of Results in Thirteen Patients with Angina Pectoris and Arteriosclerotic Heart Disease*

Case, Initials, Sex, Age	Diagnoses In Addition To Angina Pectoris and Arteriosclerotic Heart Disease	Duration of Angina Pectoris	Before, And Months After I^{131} Therapy	Usual Frequency Of Attacks Of Angina Pectoris	Basal Metabolic Rate	Serum Cholesterol	Other Findings	Comment	Therapeutic Result*
		Years			%	*mg./100 cc.*			
1. J. L. M, 41	Prior myocardial infarction	1	Before	15 daily	−10	328	ETT—32; Dyspnea; angina at night and rest		
			15	one monthly	−25	770	ETT—45†; No attacks at night or rest; no dyspnea; actively employed	Thyroid 30 mg. daily	++++
2. R. A. M, 62	Prior myocardial infarction and pulmonary edema; hypertension	3	Before	5–10 daily	−15	200	Housebound; dyspnea, parox. noct. dysp. C.T.‡ 25 sec.	Thyroid 6–12 mg. for 6 mos.	
			9	None	−20	350	Actively employed; no parox. noct. dysp. or dyspnea; C.T. 27 sec.		++++
3. J. K. M, 44	Probable prior myocardial infarction	5	Before	4–5 or more nitroglyc. tablets daily	−11	325	Parox. noct. dysp.; C.T. 12 sec.		
			7	None	−24	380	None; C.T. 33 sec.	Thyroid 6–24 mg. for 3 mos.	++++
4. H. R. M, 72	Marked congestive failure; aortic sten. and insuff.; hypertension	10	Before	Many daily	Not feasible	220	Marked dyspnea on exertion, par. noct. dysp., edema, rales		
			15	None	Not feasible	399	None	Thyroid ordered, but not taken	++++
5. M. G. M, 38	2 Prior myocardial infarctions; episodes of coronary failure	2	Before	Frequent	−3	280	Noct. angina. Unable to work; C.T. 14 sec.		
			13	None	−23	450	No noct. attacks. Doing heavy labor; C.T. 18 sec.	Thyroid 24 mg.	+++
6. S. F. M, 59	Hypertension, cardiac enlarg., congestive heart failure; chronic pyelonephritis	5	Before	2–5 weekly	+3	178	Housebound; edema of legs; palpitation; orthopnea; dyspnea; C.T. 28 sec.		
			19	Rare	−20	444	Up and about; no edema; no palpitation; less dyspnea; no orthopnea; C.T. 24 sec.	Thyroid 15 mg.	++
7. B. S.	2 Prior myocardial infarctions; hyper-	2.5	Before	4 daily	−6	275	Par. noct. dysp.; C.T. 14 sec.	Emotional lability	

M, 52	tension		17	Rare	−20	450	No par. noct. dysp.; C.T. 27 sec.	Emotional lability same. Thyroid 12–45 mg. for previous 11 mos.; now on 15 mg.	++
8. M. H. F, 65	Prior myocardial infarction; diabetes mellitus	1.5	Before	1–12 daily 11–17 nitro. weekly	Not feasible	305	Palpitation		
			8	2–5 weekly	Not feasible	540	Non	Thyroid 24 mg. daily for previous 3 mos.	++
9. M. C. M, 58	2 prior myocardial infarctions	3	Before	Frequent on moderate effort	+2	307	ETT 12–15		
			3	None		530	ETT 25		
			12	Angina recurred but less than control period	−18	380	ETT 15	Thyroid 6–36 mg.	+
10. R. S. M, 69	Hypertension; intercostal neuritis following alcohol nerve block T2–T6; prior thyroid denervation	18	Before	5–6 weekly	−25	240		Depressed	
			2.5	None	−42	430			
			12	Occasional	−25	234		Thyroid 6–12 mg.	0
11. H. Y. M, 67	Probable prior myocardial infarction	5	Before	8–10 daily	−5	207	Frequent angina at night, at rest, after meals; C.T. 30 sec.	Intermittent claudication	
			5	1 daily	−27	400	None; C.T. 29 sec. Recent exacerbation of angina on increased thyroid dosage	No change	
			15	8–10 daily	−25	285		Thyroid 50–60 mg. for previous 10 mos. Now on 30 mg.	0
12. J. E. F, 59	Prior myocardial infarction; hypertension	4	Before	2–3 daily at restricted activity	−12	210	Sedentary existence; noct. angina		
			15	No change	−30	500	Still sedentary. no noct. angina	Thyroid 36 mg.	0
13. M. S. M, 61		6	Before	5–6 per week on minimal effort or eating	−6	250	ETT 18; C.T. 26 sec.		
			12	No change on effort. None on eating	−24	400	ETT-30; C.T. 31 sec.	Thyroid 60 mg.	0

* ++++ striking; +++ excellent; ++ good; + fair; 0 not worthwhile.
† ETT-Exercise Tolerance Test stopped by fatigue; no angina.
‡ Arm to Tongue Circulation Time.

enced marked improvement. He was able to undertake much more effort despite which he used only approximately 8 nitroglycerine tablets a week. Five weeks after the fourth dose, complete disappearance of angina pectoris was observed despite the fact that he spent much of every day walking about the city in search of a job. In repeated exercise tolerance tests, forty-five to fifty trips were performed without anginal pain; the patient stopped exercise at our request or because of fatigue. His facies became myxedematous; the blood cholesterol values increased and the basal metabolic rate was −22 per cent. Desiccated thyroid, 30 mg. daily, was prescribed. At the present time he has been gainfully employed, working eight hours a day for the past seven months, experiences no angina except on very strenuous exertion, and is not troubled by symptoms of myxedema. The basal metabolic rate is maintained at −25 per cent; the serum cholesterol is 770 mg. per cent.

Comment: A 41 year old man, with almost completely incapacitating angina pectoris and an old myocardial infarction was treated with 4 doses of I^{131}. Transient hypometabolism and clinical improvement in the frequency of angina pectoris followed the first 3 doses. Myxedema followed the fourth dose and was accompanied by complete disappearance of anginal pain in daily life. Correspondingly, a marked increase in the standardized exercise tolerance test was observed. He is gainfully employed, working eight hours a day as a laboratory assistant for the past seven months. On 30 mg. desiccated thyroid, he is not troubled by symptoms of myxedema. The clinical improvement is striking.

Case 2.—Arterial hypertension; arteriosclerotic heart disease. Acute posterior myocardial infarction and pulmonary edema fourteen months before treatment. Angina pectoris of three years' duration, increasing in severity with resulting invalidism. Frequent attacks of paroxysmal nocturnal dyspnea. Myxedema induced by three doses of I^{131} with complete remission of symptoms and rehabilitation to an employed state.

Pretreatment History. R. A., a 62 year old bricklayer, B.I.H. #98406, received 24 mc. I^{131} on February 12, 1948. Nine years before treatment, he was examined because of headaches, weakness and depression. The blood pressure was 170–190/115–130. Five years before I^{131}, at the time of suprapubic prostatectomy, the blood pressure was 150/100, the heart was enlarged to the left. Three years before I^{131}, he developed mild angina pectoris and dyspnea on exertion, relieved by rest and by nitroglycerine. Fourteen months before treatment he was admitted to the hospital critically ill, with severe substernal pain, acute pulmonary edema and the characteristic clinical and electrocardiographic evidence of an acute posterolateral myocardial infarction and right bundle branch block. Thereafter, he was confined at home because even slight exertion precipitated angina. He suffered five to ten attacks of angina pectoris daily and increasing breathlessness, despite limitation of activity and the use of nitroglycerine, digitalis, various xanthines and vitamins. When examined in the Cardiac Clinic during the period before treatment, he was dyspneic, weak, unable to walk without suffering substernal pain, and had had several attacks of nocturnal dyspnea.

Pretreatment Physical Examination. The blood pressure was 160/110. The retinal vessels were somewhat narrowed and tortuous. There was moderate emphysema of the lungs. No rales were heard. The heart was enlarged to the left; the rhythm regular and there were no murmurs.

Pretreatment Laboratory Examinations. (See table 2.) The blood, urine and stool were normal. The nonprotein nitrogen was 35 mg. per cent. Electrocardiograms revealed old posterolateral myocardial infarction and right bundle branch block. The serum protein bound iodine was 5.8 gamma per cent. After an I^{131} tracer dose, the urinary excretion was 54 per cent in seventy-two hours.

Post-treatment Course. On February 12, 1948, I^{131} was administered, and again on May 27 and July 24, 1948 (table 1). In late August 1948, the basal metabolic rate, serum cholesterol and physical appearance were unchanged, but the patient was able to undertake considerable effort without angina pectoris, dyspnea or paroxysmal nocturnal dyspnea. On September 25, 1948, the serum cholesterol was 400 mg. per cent. His voice was very deep, eyes and face puffy, the hands cool and slightly moist. At this time the patient became employed, for the first time in two years, as a supervisor on a bricklaying job, requiring that he rise early, travel for one hour in a street car, walk one mile to his place of employment and be ambulatory for an eight hour day. He was able to perform these tasks without dyspnea or angina. In the ensuing six months the basal metabolic rate was consistently approximately −22 per cent and the serum cholesterol between 380 and 500 mg. per cent. The patient experienced only occasional episodes of "jumping" or "fluttering" in the chest, thought to be paroxysmal tachycardia. He stated that he experienced breathlessness on climbing three flights of stairs. In February 1949, five months after hypometabolism had become evident with an elevated serum cholesterol and a lowered basal metabolic rate, the patient complained of undue sensitivity to cold, chronic sleepiness and fatigue, muscular pains, rhinorrhea. Accordingly, 12 mg. thyroid daily was administered, with improvement in these symptoms. He returned to work. Up to the present, he experiences no precordial pain, but has some

shortness of breath on climbing, without stopping, 2 to 3 flights of stairs. There is no orthopnea, cough or paroxysmal nocturnal dyspnea nor any evidence, on physical examination, of congestive failure.

Comment: This 60 year old patient with a past history of a posterior myocardial infarction and three years of angina pectoris, dyspnea on exertion and paroxysmal nocturnal dyspnea was invalided at home for fourteen months before I^{131} treatment. Following the induction of hypometabolism, he has experienced complete freedom from precordial pain and has only slight dyspnea on climbing three flights of stairs without stopping. For 9 months since the induction of hypometabolism, he has been gainfully employed on a job requiring considerable physical and mental activity. On 12 mg. thyroid daily, the basal metabolic rate is −20 per cent, the serum cholesterol 350 mg. per cent, and he is not troubled by symptoms of hypometabolism. A striking result.

Case 3.—Arteriosclerotic heart disease; severe angina pectoris of five years' duration, preventing employment and markedly limiting activity. Probable old anterior myocardial infarction four and one-half years before I^{131}. Orthopnea and paroxysmal nocturnal dyspnea. Myxedema induced with one dose of I^{131}. Striking relief of angina pectoris.

Pre-treatment History. J. K., a 44 year old former bartender and shipyard worker, B.I.H. #A87843, received 42.4 mc. of I^{131} on January 27, 1949. Five years previously the patient first experienced characteristic angina pectoris relieved by nitroglycerine. He was hospitalized for two weeks after one episode of severe pain. Four and one-half years before treatment, recurrent attacks of angina pectoris awakened him from sleep and occurred every few hours despite frequent use of nitroglycerine. He was hospitalized at another institution for thirty days, where, following prolonged cardiac pain and dyspnea after an exercise test, electrocardiograms revealed evidence of definite myocardial damage. For eight months he had received injections of testosterone without relief; theobromine sodium acetate and digitalis were also without benefit. Anginal attacks, accompanied frequently by dyspnea and occasionally by nausea and vomiting, were precipitated by as little effort as dressing or undressing, excitement, cold, or meals. He had attacks awakening him from sleep. He had been unable to work because even a limited amount of effort produced pain; he invariably developed an anginal episode on walking more than one block. The average intake of nitroglycerine was four to five tablets daily; in the period before treatment the attacks were increasing in frequency. For the five years before treatment he had also experienced dyspnea on exertion, orthopnea requiring three pillows and had had two episodes of paroxysmal nocturnal dyspnea.

Pretreatment Physical Examination. The thyroid was not palpable. Blood pressure was 130/80. The heart was enlarged to the left; the rhythm was regular. There was a soft aortic systolic murmur. The lungs were clear. The non-tender liver was felt two fingersbreadth below the right costal margin. Spleen was not palpable.

Pretreatment Laboratory Data. (See table 2.) The blood and urine were normal. The electrocardiogram was consistent with an old anterior myocardial infarction. On x-ray the heart shadow was increased. Circulation time was twelve seconds. After an I^{131} tracer dose, the urinary excretion was 58 per cent in seventy-two hours.

Post treatment History. On January 27, 1949, 42.5 mc. of I^{131} were given. Three days later he developed a painful throat, with thyroid gland tenderness. The pharynx was normal. During the next week chills, nausea, and vomiting, and increased throat pain were experienced. The thyroid gland was two times normal size, firm and acutely tender. In this period, i.e., two to three weeks after treatment, the patient observed increased angina pectoris. Despite marked restriction of activity, four or five attacks occurred daily; the slightest effort produced an attack. It was believed that the patient had experienced thyroiditis with mild thyrotoxicosis, manifested by a rise in the basal metabolic rate and a drop in the serum cholesterol (fig. 1), accompanied by increased angina pectoris. During the next one to two weeks this reaction gradually subsided and the serum cholesterol, basal metabolic rate and the severity of the angina pectoris were approximately the same as before treatment (fig. 1). Eight weeks after I^{131}, the patient noted that for the first time in five years he was able to go for a number of days without requiring any nitroglycerine. He had no night pain, no meal pain, no prolonged pain and was able to undertake more effort without developing angina. During the the prior five years he had never experienced a comparable remission. The basal metabolic rate was −24 per cent and the serum cholesterol was 400 mg. per cent. He showed no clinical evidence of myxedema. During the next few weeks further improvement was noted and he went an entire week without taking nitroglycerine. He was able to walk three blocks rapidly without pain; he dressed and undressed without pain and he had no pains at meals, at night or during conversations; all had previously precipitated attacks. Fourteen weeks after treatment, six weeks after the onset of improvement, the patient observed weakness of the hands, fatigability and postnasal discharge. The cholesterol was 625 mg. per cent and the basal metabolic rate was −25 per cent. His face appeared fuller and less florid. During the next week he noted loss of energy,

marked weakness, fatigability, rhinorrhea, sleepiness and nasal speech. On 24 mg. of thyroid daily these symptoms disappeared. The basal metabolic rate was −24 per cent and the serum cholesterol was 380 mg. per cent.

Comment: This 44 year old patient had had angina pectoris for five years, a probable acute anterior myocardial infarction and two episodes of paroxysmal nocturnal dyspnea. Anginal attacks were produced by minimum effort such as walking one block or undressing; they occurred at night and after meals and required four to five nitroglycerine tablets daily. He had experienced no remission during this entire period. With the induction of hypometabolism after I^{131} the patient noted no night pain or meal pain and went long periods without any anginal episodes or paroxysmal nocturnal dyspnea. He required only about one nitroglycerine tablet every twenty days. His exercise tolerance was increased from one to three and one-half blocks, and he can perform all his usual tasks about the house without development of angina pectoris. No symptoms referable to hypometabolism are present on a daily dosage of 24 mg. of thyroid. The relief from angina pectoris is striking.

Case 4.—Arteriosclerotic heart disease; aortic stenosis and insufficiency; auricular fibrillation; angina pectoris of ten years' duration of increasing severity; marked congestive heart failure refractory to all accepted types of therapy. Paroxysmal nocturnal dyspnea. Induction of myxedema with one dose of I^{131}. Complete remission of symptoms of both angina pectoris and congestive failure past twelve months. Striking therapeutic result.

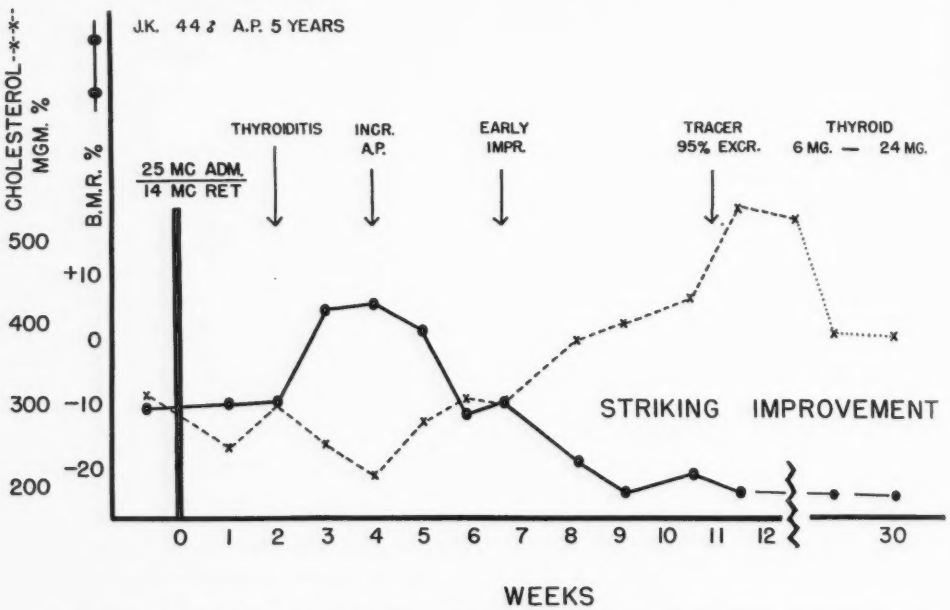

FIG. 1.—J. K., Case 3. The serum cholesterol, the basal metabolic rate and the clinical course following the administration of 42.5 millicuries I^{131}. To conform to the activity of the millicurie used by the Bureau of Standards and also used throughout this paper, the millicurie stated in the above figure should be multiplied by the factor of 1.7.

Pretreatment History. H. R., a 72 year old white male, B.I.H. #98225, received 25.5 mc. of I^{131} on February 26, 1948. Ten years before, the patient had noted precordial pain on slight exertion and on walking upstairs, gradually increasing in severity. During the seven years before treatment, he was observed in the Cardiac Clinic. Three years before I^{131} therapy, increasing frequency of angina on the slightest exertion, and even when at rest, was associated with dyspnea and ankle edema. At this time, fine moist rales were heard at both bases. The tender liver edge was felt three fingers below the right costal margin. The patient was maintained on digitalis, theobromine sodium acetate and nitroglycerine. Eighteen months before treatment, anginal attacks

occurred on effort and at rest, and as often as five to six times nightly, accompanied by dyspnea. Ankle edema was present. The blood pressure was 150–200/50–90. There was a loud, musical, apical systolic murmur, obscuring the first sound, and a loud, high pitched aortic systolic murmur transmitted to the neck vessels and the right upper back. There was a short aortic diastolic murmur. The second aortic sound was diminished. A diagnosis of aortic stenosis and insufficiency was made. Fifteen months before treatment, auricular fibrillation was observed.

During the year before I^{131}, dyspnea became markedly worse and he became short of breath on walking fifteen steps. On a rice diet regimen, he appeared to show some improvement, with diminution in exertional dyspnea and relief of angina, but was unable to maintain the diet. Five months before I^{131}, he again suffered angina and dyspnea on the slightest exertion. Despite theobromine sodium acetate, digitalis and mercurial diuretics by mouth and intravenously during the period immedialy preceding I^{131}, increasing dyspnea, paroxysmal nocturnal dyspnea, ankle edema and very frequent attacks of angina pectoris were noted.

Pretreatment Physical Examination. The patient was dyspneic, cyanotic and the neck veins were distended. There were rales at both lung bases. The heart was enlarged to the left; the rhythm was grossly irregular with a ventricular rate of 68. The signs of aortic stenosis and insufficiency were noted. The tender liver edge was palpable three fingers below the right costal margin. There was 2+ pitting edema at the ankles. The blood pressure was 185/65.

Post-treatment Clinical Course. On February 26, 1948 the patient received 25.5 mc. of I^{131}, followed a week later by sore throat on swallowing which gradually decreased during the next two weeks. In June 1948, four months after treatment, he reported conspicuous improvement. He had no exertional dyspnea, "could walk for two hours and could run without short breath." He had had no chest pain whatsoever. He had discarded all medication. Physical examination showed no venous distention, a few, medium rales at the right base, a barely palpable nontender liver and only minimal ankle edema. There was no clinical evidence of myxedema, and the patient refused basal metabolic studies. The serum cholesterol had risen from 220 to 283 mg. per cent. During the following two months the patient maintained this improvement, the basal rales cleared and, for the first time in a long period, he could sleep flat in bed. He had no cough, no dyspnea and no angina pectoris. The serum cholesterol had risen to 331 mg. per cent. His skin was cool and there was some puffiness below the eyes. On August 9, 1948, five and a half months after I^{131}, the patient showed definite evidence of myxedema. He had maintained his cardiac improvement. At this time, he was instructed to take thyroid 6 mg. daily, and later this was increased to 18 mg. However, he continued to complain of symptoms due to myxedema, and it was discovered that the patient had failed to take thyroid as ordered. In May 1949, the patient was seen because of severe pain in the right upper quadrant, due to herpes zoster. At this time he was having no angina pectoris and no symptoms of congestive failure. He was taking no cardiac medication or thyroid. He had no dyspnea, orthopnea, ankle edema and suffered minimal discomfort from myxedema. X-ray examination showed the heart to be greatly dilated with small amplitude of contraction. The heart rhythm was grossly irregular, rate 57 to 110, and the electrocardiogram showed auricular flutter with varying auriculo-ventricular block. The serum cholesterol was 399 mg. per cent.

Comment: This 72 year old male, with a ten year history of angina pectoris and an eight year history of congestive heart failure, showed striking improvement following the administration of radioactive iodine with remission of all his cardiac symptomatology. Five and one-half months after treatment, he went into frank myxedema, the symptoms of which were troublesome, but the patient refused to take thyroid as ordered. When last seen, fifteen months after I^{131}, he had maintained his cardiac improvement and was only minimally troubled by myxedema. He has continued to refuse to take thyroid.

Case 5.—Severe, frequent angina pectoris, two years. Two attacks of acute myocardial infarction and many other attacks of excruciating and prolonged cardiac pain without electrocardiographic changes, i.e., "coronary failure." Myxedema induced by two doses of I^{131} with marked relief of angina pectoris. Myxedema controlled by 24 mg. of thyroid daily. Doing heavy work and gainfully employed for past eight months. Excellent therapeutic result.

Pretreatment History. M. G., a 38 year old painting and construction supervisor, B.I.H. #92857, received 42.5 mc. of I^{131} on June 4, 1948. Beginning in June 1946, attacks of mild substernal pressure occurred following meals, exercise and emotional disturbance and also occasionally awakened the patient from sleep. The first hospital admission in February 1947 had been preceded by marked increase in severity and duration of attacks which culminated in acute posterior myocardial infarction attended by shock, a pericardial friction rub, electrocardiographic changes, fever, leukocytosis and increased corrected sedimentation rate. He was hospitalized for six weeks. After discharge from the hospital, the attacks of angina pectoris continued

with increased severity, and were associated with nausea, heartburn and epigastric fullness. During the fifteen months prior to I^{131}, the patient had many severe and excruciating attacks of cardiac pain during the night as well as during the day, only slightly relieved by nitroglycerine and preventing steady employment. Nine months prior to I^{131} he suffered an acute anterior myocardial infarction, and on two subsequent occasions he was similarly hospitalized because of severe prolonged cardiac pain, although serial electrocardiographic changes were graphic tracings were consistent with old posterior and anterior myocardial infarcts. X-ray examination revealed the left ventricle slightly enlarged to the left.

Post-treatment Course. The patient received 42.5 mc. of I^{131} on June 4, and 25.5 mc. on July 23, 1948 (fig. 2). During the second week after the first dose he noted profuse perspiration, increased palpitation and dyspnea and more frequent severe attacks of angina pectoris. The skin was warm and flushed; the thyroid palpable and very tender. The basal met-

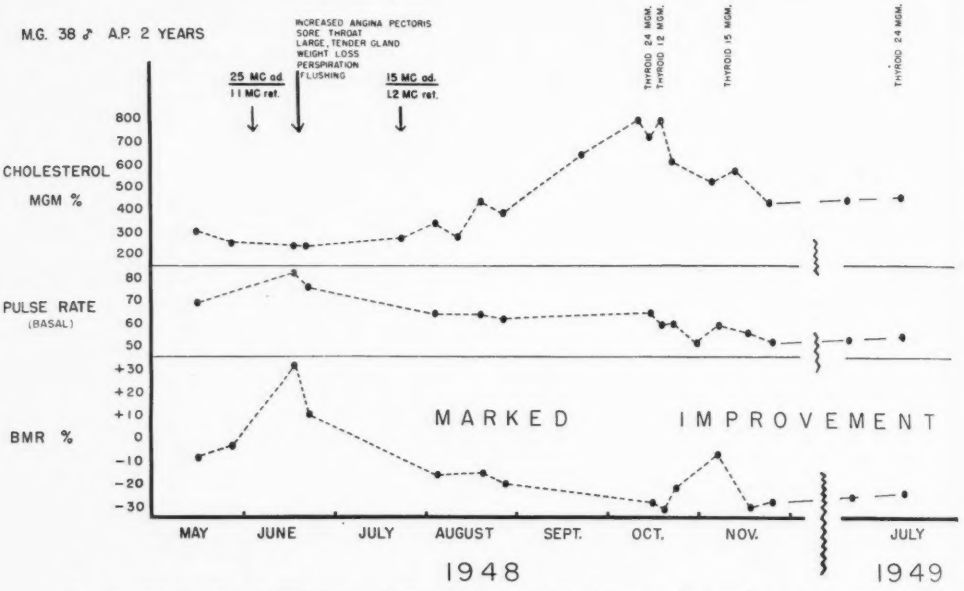

FIG. 2.—M. G., Case 5. The serum cholesterol, the basal pulse rate, the basal metabolic rate and the clinical course following the administration of two doses of 42.5 and 25.5 millicuries of I^{131}. To conform to the activity of the millicurie used by the Bureau of Standards and also used throughout this paper, the millicurie stated in the above figure should be multiplied by the factor of 1.7.

not evident on these latter two admissions; minor T wave changes were observed.

During the hospital admission immediately before I^{131}, the patient was placed on dicumarol[25–27] and maintained at a satisfactory prothrombin time level with 50 mg. alternating with 100 mg. daily. The number and severity of attacks of angina pectoris became somewhat less on complete bed rest but did not disappear. All other medical measures having failed, it was decided, despite the grave prognosis, to administer I^{131}.

Pretreatment Physical Examination. The findings were normal. The heart was not enlarged; the sounds were of good quality; no murmurs were heard. The blood pressure was 122/84.

Pretreatment Laboratory Examinations. (Table 2.) The blood and urine were normal. Electrocardio-

abolic rate was +30 per cent, the basal pulse rate 85 (fig. 2); the circulation time was 13 seconds; the serum cholesterol 230 mg./100 cc. This was attributed in part to the release of thyroid hormone because of the destructive action of I^{131} on the thyroid gland. The symptoms and signs of hypermetabolism subsided and the patient reverted to pretreatment status in respect to his angina pectoris.

On June 26, 1948, three weeks after I^{131}, the patient was admitted to the hospital for the fifth time because of severe prolonged precordial pain lasting three hours, associated with nausea, due to an acute posterolateral myocardial infarct. Dicumarol therapy was continued. During the fourth week of hospitalization, the patient experienced relief from cardiac pain and stated that he felt better than he had in a long time. At home he continued to show

clinical improvement, was able to undertake considerably more effort and had only occasional slight momentary sticky pain not related to effort or emotion. He observed increased tolerance to hot weather and no pain on exertion or emotion. On August 4, nine weeks after the first dose and twelve days after the second dose, the basal metabolic rate was −17 per cent; the serum cholesterol values rose to approximately 400 mg. per cent. He re-entered the hospital, however, for the sixth time on September 1, 1948, because of severe persistent chest and left axillary pain. Electrocardiographic and other laboratory studies failed to reveal any evidences of fresh involvement of the myocardium. Dicumarol therapy was continued.

Four months after the first dose the cholesterol was 700 mg. per cent and the basal metabolic rate −30 per cent. On 12–24 mg. of thyroid he experienced a variable amount of disability from myxedema, feeling perfectly well on some occasions and complaining of symptomatology on others. The patient was subject to a high degree of emotional stress and aggravation and continued to have atypical precordial pain. The precordial symptoms were unusual in that they did not occur on undertaking even fairly severe work but rather occurred at the end of the day when the patient sat down to rest. It was the opinion of a number of observers that these precordial sensations were not of cardiovascular origin.

In April 1949, eleven months after the first dose, he went to work in another city and dicumarol was stopped. Despite marked physical labor including the lifting of heavy materials up to 50 lbs. in weight, and working at least eight hours daily, the patient experienced no chest pain and did not tire easily until he returned to the region of his home, when he again began to experience fleeting momentary stabbing precordial pain. At the present time, thirteen months after the first dose of I^{131}, he is receiving thyroid 24 mg. daily and has no troublesome symptoms from hypothyroidism.

Comment. This 38 year old man with severe disabling angina decubitus was incapacitated during the fifteen months prior to I^{131}. He obtained almost complete freedom from cardiac pain following the induction of myxedema by I^{131}. He has been gainfully employed at heavy manual labor for the past eight months. He experiences fleeting momentary stabbing precordial pain, unrelated to effort and occurring at the end of the day when resting. On 24 mg. thyroid daily he has no troublesome symptoms of hypothyroidism. An excellent result.

Case 6.—Recurrent acute pyelonephritis; hypertension and cardiac hypertrophy; angina pectoris and congestive heart failure with orthopnea for five years. Induction of myxedema with one dose of I^{131} with marked decrease of angina pectoris and improvement in congestive heart failure. Minimal discomfort from hypothyroidism. Good, worthwhile therapeutic result.

Pretreatment History. S. F., a 59 year old insurance and real estate agent, B.I.H. #62797, referred through the courtesy of Dr. Paul M. Zoll, received 42.5 mc. of I^{131} on December 30, 1947. In September 1942, he noted the onset of dyspnea on exertion, and angina pectoris on exertion and emotion, relieved by nitroglycerine. There was a past history of recurrent, acute pyelonephritis. Physical examination revealed the blood pressure 194/128, cervical venous engorgement, and fine basal rales. The liver was four fingers below the costal margin and there was slight pitting edema of both ankles. On rest, digitalization, theobromine sodium acetate and phenobarbital, he noted some improvement in dyspnea. Attacks of angina pectoris continued and he was unable to work.

In June 1947 he suffered an exacerbation of congestive failure with orthopnea and peripheral edema. Walking even short distances produced dyspnea and palpitation. Although house bound, he suffered two to five attacks of angina pectoris weekly.

On a chair-and-bed regimen, digitalis and a low salt diet, purines and nitroglycerine for the three months before I^{131} therapy, there were continued peripheral edema, dyspnea on climbing one flight of stairs, orthopnea and palpitation. Attacks of angina pectoris continued unchanged.

Pretreatment Physical Examination. The neck veins were distended, the lungs were clear. The heart was enlarged, the rhythm regular. The blood pressure was 228/118. The liver was percussed three fingersbreadth below the costal margin. There was moderate pitting edema of the legs.

Pretreatment Laboratory Examination. (See table 2.) The blood was normal. The urine showed a 1 + albumin content and 0–3 red blood cells in the sediment. The specific gravity was 1.016. The electrocardiogram was consistent with left ventricular hypertrophy. On x-ray examination the heart was markedly enlarged to the left, the aorta dilated and the hilar shadows and lung markings increased, indicating left ventricular hypertrophy and dilatation and moderate pulmonary congestion.

Post-treatment Course. I^{131} was administered December 30, 1947; ten days later he noted sore throat, pain on swallowing and slight cough, but no thyroid tenderness or swelling. Three serum cholesterol measurements during the next six weeks were 178, 177 and 178 mg. per cent. Approximately 13 weeks after I^{131} the basal metabolic rate was −25 per cent, the serum cholesterol 340 mg. per cent. A tracer dose of I^{131} was followed by a urinary excretion of 81 per cent during the next three days. Thyroid 15 mg. daily was prescribed and discomfort from hypothyroidism became minimal. Associated with the

hypometabolic state, there was distinct improvement with absence of palpitation, lessened dyspnea and disappearance of peripheral edema. A definite decrease in the number of attacks of angina pectoris occurred; nitroglycerine consumption decreased from 2 to 5 tablets per week to 2 tablets per month. There was, moreover, considerable concomitant increase in the amount of activity, in that he was leaving the house and undertaking considerable exertion.

With an increase in thyroid to 24 mg. daily in August 1948, angina pectoris and congestive failure increased, and he suffered an attack of paroxysmal nocturnal dyspnea. In September 1948, nine months after I^{131}, he suffered a cerebrovascular accident but recovered with little residual disability. Thereafter he remained at home, except for trips to the hospital, until recently, when he has increased his activity and taken short walks. Thyroid dosage was reduced to 15 mg. daily. In the ten months since the cerebrovascular accident, he has had only a rare episode of angina pectoris, has had no orthopnea, dyspnea, ankle swelling, cough or paroxysmal nocturnal dyspnea. X-ray examination showed the heart size to be unchanged and the lungs clear.

Comment: A 59 year old man with marked hypertension, congestive failure and angina pectoris, complicated by chronic renal disease, received one dose of I^{131}. Myxedema was induced with concomitant decided improvement in congestive failure and in angina pectoris. On a dosage of 15 mg. thyroid daily, there has been minimal discomfort from hypometabolism, congestive failure is absent, orthopnea has disappeared and only a rare attack of angina pectoris is experienced. The result is considered good and worthwhile.

Case 7.—Arterial hypertension; arteriosclerotic heart disease. Angina pectoris of two and one-half years' duration. Two attacks of acute myocardial infarction, fifteen and six months before treatment. Orthopnea, paroxysmal nocturnal dyspnea. Myxedema induced by two doses of I^{131} with relief of the symptoms of angina pectoris but some discomfort from the hypometabolic state. Good, worthwhile result.

Pretreatment History. B. S., a 52 year old white man, B.I.H. # M2922, received 25.5 mc. I^{131} March 11, 1948. Two and one-half years before treatment severe angina pectoris developed once or twice daily, precipitated by effort, and relieved by rest and nitroglycerine. Fifteen months before treatment, increasingly frequent angina pectoris culminated in an attack of severe and prolonged cardiac pain, weakness, sweating, collapse, slight fever and electrocardiographic tracings characteristic of acute posterior myocardial infarction. After discharge, he had frequent attacks of angina pectoris, with dyspnea on minimal effort such as bending over to tie his shoes, or having a bowel movement. The patient was orthopneic and experienced several attacks of paroxysmal nocturnal dyspnea. Six months before I^{131}, a second episode of severe precordial pain lasting twenty minutes occurred, with electrocardiographic changes of anterior myocardial infarction. During the period of pretreatment study, various observers noted emotional lability, anxiety, easy fatigability, weakness, occasional dizziness and marked hyperventilation. Despite frequent angina pectoris he continued to do light work three to four hours daily.

Propylthiouracil, 500 mg. daily, was administered for two weeks before I^{131} therapy, but had to be discontinued because of leukopenia.

Pretreatment Physical Examination. The arterioles of the fundi showed increased tortuosity and narrowing. The blood pressure was 170/100. The heart was enlarged to the left, the rhythm regular, the sounds normal. There was a short, Grade I apical systolic murmur. There was moderate pulmonary emphysema. The tender liver was felt two to three fingersbreadth below the right costal margin. The spleen was felt two fingersbreadth below the left costal margin.

Pretreatment Laboratory Data. (See table 2.) The blood and urine were normal. Complete gastrointestinal and gall-bladder x-ray examinations were normal. Chemical tests of liver function were within normal limits. During the seventy-two hours after a tracer dose of I^{131} he excreted 79 per cent in the urine. The electrocardiogram was abnormal; the pattern was not diagnostic.

Post-treatment Clinical Course. On March 11, 1948, he received 25.5 mc. and on May 27, 1948, 27 mc. of I^{131} (table 1). On July 7, 1948, coincident with evidence of slight myxedema and serum cholesterol 400 mg. per cent (table 2), angina pectoris markedly decreased and he required no nitroglycerine for several weeks despite at least the same level of activity. There were no further attacks of paroxysmal nocturnal dyspnea and no orthopnea. During the next two months, he continued to experience conspicuous relief of angina pectoris. In September 1948 he had considerable discomfort from myxedema and many precordial sensations different from those previously experienced on effort and not relieved by rest or nitroglycerine. On thyroid, 12 mg. daily, the serum cholesterol decreased from over 600 to 360 mg. per cent. He also complained of right upper abdominal tenderness and pain. After thorough study in the hospital the consensus was that many of the symptoms were on a functional basis. It was, however, decided to re-establish the euthyroid state to learn the degree to which the symptoms were due to myxedema. Accordingly, the thyroid dose was gradually increased to 45 mg. daily. After three weeks the patient complained of increased frequency of angina pectoris, and required

about 6 nitroglycerine tablets daily. He noted diminution of numbness of the hands and feet, but most of the symptoms, notably fatigue and hyperventilation remained. At this time, the patient stated unequivocally that he would prefer having such hypometabolic symptoms as were necessary rather than the pain in the chest, which, by this time, was recurring on minimal effort. After reduction to 15 mg. thyroid daily, there was an increase in serum cholesterol, lowered basal metabolic rate, and definite diminution in angina from three to five attacks daily, to only that number per week, or less. There was, however, increased fatigability and stiffness and numbness of the hands.

Comment: While myxedematous, this patient was free of angina pectoris, paroxysmal nocturnal dyspnea and orthopnea but suffered from a number of symptoms, some of which could possibly be ascribed to hypometabolism. On increasing the thyroid to 45 mg. daily, he noticed a decrease of the numbness of the hands, paresthesias and some of the dizziness. Concomitantly, however, the angina pectoris returned to the pretreatment control severity. The patient unequivocally stated he preferred the hypometabolic symptoms to his chest pain. The dose of thyroid was then decreased to 15 mg. daily and the basal metabolic rate fell to −20 per cent and the serum cholesterol rose again to 450 mg. per cent. With this there was a marked diminution in the angina pectoris. Despite return of numbness and fatigability, the improvement in angina pectoris during the past eleven months was such that the patient and observers regarded the result as having been worthwhile.

Case 8.—Severe diabetes mellitus for twenty years. Angina pectoris for eighteen months. Acute myocardial infarction one year before treatment, followed by increased frequency and intensity of angina pectoris. Myxedema induced by two doses of I^{131} with marked decrease of angina pectoris and lessened insulin requirement. Some discomfort from myxedema. Good therapeutic result.

Pretreatment History. M. H., a 65 year old housewife, B.I.H. #72724, received 39 mc. I^{131} on November 6, 1948. She had had diabetes for twenty years, observed in the Diabetic Clinic for 18 years, requiring increasing doses of insulin until, at the time of I^{131} treatment, she was maintained under irregular control by 56 units of protamine and 20 units of regular insulin daily. Eighteen months before treatment the patient noted substernal pressure radiating to both shoulders, precipitated by exertion, and relieved by rest or by nitroglycerine. One year before I^{131} she was hospitalized for nine weeks because of acute myocardial infarction. Three months before treatment, examination in the Cardiac Clinic revealed frequent palpitation and attacks of angina pectoris one to twelve times daily on emotion, on slight exertion, aggravated by cold, and of much greater frequency and severity than before the acute myocardial infarction. The average weekly requirement of nitroglycerine varied from 11 to 17 tablets.

Pretreatment Physical Examination. The thyroid was not palpable. The heart was enlarged. The sounds were of good quality. There was a Grade II systolic murmur loudest in the pulmonic area and the rhythm was regular. The blood pressure was 130/80. The lungs were clear.

Pretreatment Laboratory Examinations. (See table 2.) The blood was normal. The urine showed 1+ albumin and rare red blood cells. On x-ray examination the heart was slightly enlarged and the lungs clear. Electrocardiogram was consistent with old posterior myocardial infarction and left ventricular hypertrophy. The P-R interval was 0.22 second. Because of the severity of the diabetes and our unwillingness to allow the patient to fast, basal metabolism studies were not performed. Nonfasting serum cholesterol three hours postprandially on a standard diabetic diet was 335 and 395 mg. per cent. Following a tracer dose of I^{131} the patient excreted 62 per cent in the urine in seventy-two hours.

Post-treatment Clinical Course. On November 6, 1948 she received 39 mc. and on January 21, 1949, 34 mc. I^{131} (table 1). Three weeks after the first dose, a nontender nodule 1.5 cm. in diameter became palpable at the left lower pole of the thyroid. During the next month, the nodule gradually decreased in size and disappeared. In April 1949, ten weeks after the second dose, the patient definitely experienced fewer episodes of squeezing precordial pain and they were less severe. There was also a diminution in palpitation. The serum cholesterol had risen 100 mg. per cent from the previous level. Six weeks later, four months after the second dose, the patient noted further marked improvement and required nitroglycerine only once every two to three weeks. Furthermore, the urinary reductions of Benedict's solution were negative more frequently than ever before, and the Diabetic Clinic in consequence reduced the daily dose of insulin from 56 units of protamin insulin and 20 of regular insulin in the morning to 50 units of protamine insulin and 12 of regular insulin. The serum cholesterol was 540 mg. per cent. While extremely grateful for the relief of angina the patient noted many symptoms of myxedema, which were ameliorated by 24 mg. of thyroid daily. On this dosage she began to experience occasional mild episodes of angina pectoris requiring 2 to 5 nitroglycerine tablets weekly as compared with 11 to 17 tablets a week prior to I^{131}.

Comment: This 65 year old woman with angina

pectoris and severe diabetes mellitus was treated with two doses of I^{131}. Myxedema was induced with marked improvement of angina pectoris, relief of palpitation and some amelioration of diabetes mellitus. On a dose of 24 mg. thyroid daily, discomfort from hypometabolism is slight and angina pectoris has remained greatly improved. This patient is considered a good therapeutic result.

Case 9.—Arteriosclerotic heart disease. Two prior attacks of acute myocardial infarction. Angina pectoris for three years before I^{131}. Induction of myxedema with I^{131}. Relief of angina pectoris and increased exercise tolerance tests for nine months. Diminished improvement with increase in thyroid medication. A worthwhile result.

Pretreatment History. M. C., a 58 year old former painter, B.I.H. #40803, received 15.5 mc. I^{131} on August 9, 1948. Ten years before treatment he experienced an episode of acute posterior myocardial infarction. Thereafter, he was disabled by a variety of complaints, regarded as functional. Four years before I^{131} he was awakened from sleep by severe epigastric pain and chest pressure and was hospitalized for five weeks with acute myocardial infarction. Thereafter, the patient was disabled because of angina pectoris on slight effort such as bending over a bath tub or walking a little faster than usual, or on excitement. The pain lasted " one to two minutes" and was relieved by rest and somewhat by nitroglycerine. The number of attacks a day was directly related to the level of effort and in consequence he lived a very restricted existence. Several xanthine preparations and quinidine were without effect on the exercise tolerance or on attacks suffered in daily life.

Pretreatment Physical Examination. The thyroid was barely palpable and non-nodular. The blood pressure was 140/80. The heart was not enlarged. The rhythm was regular. The sounds were of good quality and no murmurs were heard.

Pretreatment Laboratory Data. (See table 2.) The blood and urine were normal. Electrocardiograms revealed old, posterior myocardial infarction and bundle branch block. X-ray examination showed the heart to be of average size and shape. There were marked degenerative changes of the thoracic spine with narrowing of the 5th and 6th discs.

Post-treatment Course. The patient received 15.5, 24 and 32 mc. I^{131} on August 9 and 24 and September 30, 1948, respectively (table 1). On September 30, seven weeks after the first treatment, the patient noted fatigue, hoarseness, some puffiness of the eyes. In the middle of October 1948, nine weeks after the first dose, he noted freedom from angina pectoris. The standardized exercise tolerance test was unchanged. Shortly thereafter, the patient became frankly myxedematous; the serum cholesterol rose to 530 mg. per cent. He remained free of angina pectoris and the standardized exercise tolerance test was twenty-one to twenty-five trips. On increased doses of thyroid from 6 to 36 mg. the symptoms of myxedema were relieved (table 2). Angina pectoris recurred, less frequent than before I^{131}, and the exercise tolerance test was fifteen trips.

Comment: A 58 year old man with two previous myocardial infarctions and angina pectoris of three years' duration received three doses of I^{131}. Myxedema was induced and angina pectoris was ameliorated. It was the independent observation of the Head of the Cardiac Clinic, Dr. Paul M. Zoll, "that the patient was unquestionably considerably improved. His angina pectoris was completely absent for several months and now occurs only infrequently. He is able to do much more than previously. There are no symptoms directly referable to myxedema at present, unless some of the fatigue is on this basis. The therapy was certainly worthwhile for this patient."

Case 10.—Angina pectoris for eighteen years before treatment. Paravertebral alcohol block with postinjection neuritis twelve years before I^{131}; denervation of thyroid gland eleven years before I^{131}. Myxedema induced by radioactive iodine. Therapeutic effect not considered worthwhile.

Pretreatment History. R. S., a 69 year old male clothing cutter, B.I.H. #M1052, received 30.5 mc. I^{131} on December 31, 1947. In 1930 and 1931 he was hospitalized for five and seven months, respectively, because of status anginosus. In 1935 and 1936, paravertebral alcohol injection (T2–T5) and thyroid denervation, respectively, were without benefit. During the previous thirteen years under the close supervision of the Angina Pectoris Clinic, approximately sixty medications were tried without significant benefit. During this entire period there had been no remission from angina pectoris for more than one week.

During the nine months before I^{131} treatment he suffered a severe reactive depression and anxiety, had numerous nightmares accompanied by angina pectoris and twice attempted suicide. Although in bed the greater part of the time, he still suffered approximately one attack daily.

Pretreatment Physical Examination. The blood pressure was 150/84. The heart was not enlarged; the rhythm, regular. There was a Grade II apical systolic murmur. The lungs were clear.

Pretreatment Laboratory Data. (See table 2.) The urine and blood were normal. The serology was negative. X-ray of the heart and the electrocardiogram were within normal limits. Following a tracer

dose of I^{131}, 57 per cent was excreted in the urine in three days; two additional tracer studies were similar.

Post-treatment Course. In 1935 this patient had been studied and rejected for total thyroidectomy because of a basal metabolic rate of −22 per cent. Although improvement after I^{131} was considered likewise unlikely, the absence of symptoms of hypothyroidism, the euthyroid tracer excretions, and the failure of all other treatment led us to accept this patient on an investigative basis. Accordingly, on December 1, 1947, the patient received 30.5 mc. I^{131} (table 1). Ten weeks later the metabolic rate was −42 per cent, the serum cholesterol 430 mg. per cent and the patient showed marked evidence of hypothyroidism. Anginal pain had not been experienced since the first week after I^{131}. The exercise tolerance test, however, was unchanged. Following the administration of thyroid, 6 to 12 mg. daily, the clinical signs of hypothyroidism were ameliorated and the basal metabolic rate rose to −25 per cent; the serum cholesterol fell to 234 mg. per cent. During this period, the patient suffered an occasional attack of angina pectoris. He was, however, continually depressed, brooding, not interested in living and, in November 1948, approximately one year after I^{131} therapy, he expired, following an overdose of a sedative in what was apparently suicide.

Comment: A patient with severe, disabling angina pectoris of eighteen years' duration, emotional instability and low metabolic rate was given I^{131} in December 1947. Marked hypothyroidism followed and was associated with an absence of attacks in daily life. The exercise tolerance test was not significantly changed and, following the administration of small doses of thyroid, attacks of angina pectoris recurred. In evaluating the effect of hypothyroidism in this patient, we consider that the procedure has not been beneficial to this patient and the result not worthwhile. This experience again emphasizes that low pretreatment metabolic rates and severe emotional instability constitute contraindications to this form of therapy.

Case 11.—Arteriosclerotic heart disease, probable old myocardial infarction, angina pectoris of increasing severity for five years, refractory to all types of treatment. Myxedema induced with I^{131} with some relief of angina pectoris but with uncomfortable symptoms of myxedema. Result considered not worthwhile.

Pretreatment History. H. Y., a 67 year old upholsterer, B.I.H. # M2457, received 25.5 mc. I^{131} on April 13, 1948. Five years before treatment probable acute myocardial infarction occurred. Thereafter, angina pectoris became increasingly severe and frequent with as many as 10 to 15 attacks a day. During the three years before treatment under close supervision of the Angina Pectoris Clinic, various xanthines, Khellin, vitamin E, potassium iodide, and digitalis were administered without effect. Only nitroglycerine was of value. Eight months before treatment the patient experienced pain in the calf and anterior aspects of the legs on effort. At the time of treatment he was taking at least 8 to 10 nitroglycerine tablets every day, and had angina on slight effort, at rest, at night and with meals.

Pretreatment Physical Examination. The heart was enlarged, the left border 13 cm. from the midsternal line; the rate was 80; the rhythm regular; the sounds were of good quality; no significant murmurs were heard. Blood pressure was 130/80. The chest was emphysematous. A few scattered moist rales were heard at the right base posteriorly. There was no peripheral edema.

Pretreatment Laboratory Data. (See table 2.) The blood and urine were normal. The electrocardiogram was consistent with old anterior myocardial infarction.

Post-treatment Clinical Course. On April 13, 1948, the patient received 25.5 mc. of I^{131} (table 1). Two months later the basal metabolic rate was −11 per cent; the patient observed he had the same number of attacks but they were less severe. Nocturnal attacks decreased from nightly to only once a week and he could walk a little farther without developing pain. Exercise tolerance test was unchanged.

Four months after I^{131} the basal metabolic rate decreased to −17 per cent. The serum cholesterol rose to 328 mg./100 cc. The patient required only 2 to 5 nitroglycerine tablets a day and none at night. He no longer had attacks at meals, but climbing stairs continued to induce angina pectoris. During the next month, frank myxedema occurred; the metabolism was −27 per cent, the cholesterol 400 mg. per cent. During this period there was marked diminution of angina on effort. Nitroglycerine tablets, 3 daily, were used only in an attempt to alleviate intermittent claudication. Exercise tolerance test was not of value because of the leg pain. Thyroid, 24 to 36 mg. a day, did not control the symptoms of hypothyroidism. Despite the fairly marked improvement in angina pectoris as manifested by diminution in the number of attacks from ten to fifteen to only one to two a day, the absence of night pain, and the ability to work several hours a day without pain, the patient was unhappy over the degree of discomfort arising from myxedema. On thyroid, 45 to 60 mg. daily, gradual loss of the uncomfortable symptoms of myxedema and a concomitant return of angina pectoris to the pretreatment level occurred. Intermittent claudication remained troublesome.

Comment: Angina pectoris was greatly lessened in the presence of myxedema, but when thyroid was administered to ameliorate the symptoms of

hypothyroidism, angina pectoris returned and was approximately that obtaining before treatment. The therapeutic result was considered not worthwhile.

Case 12.—Hypertension, arteriosclerotic heart disease, increasingly frequent and severe angina pectoris for three years. Acute myocardial infarction one year before treatment. Myxedema induced by one dose of I^{131}. No significant relief of angina pectoris. Therapeutic result not worthwhile.

Pretreatment History. J. E., a 59 year old female, B.I.H. #M265, received 25.5 mc. of I^{131} on May 13, 1948. She had had hypertension for eight years and angina pectoris for four years before I^{131} therapy. Attacks of angina pectoris occurred not only on walking but on eating, exposure to cold and frequently without evident precipitating factors; she was occasionally awakened from sleep by nocturnal attacks. For the three years before treatment the patient, although sedentary, had been incapacitated by angina. In January 1945, severe attacks of substernal pain lasting three to four hours were diagnosed as coronary failure. In March 1947 the patient suffered an acute anterior myocardial infarction. For one year before I^{131} the patient had had mild diabetes requiring no insulin.

Pretreatment Physical Examination. The blood pressure was 170/90. The cardiac rhythm was regular with an occasional ventricular premature beat; sounds were of good quality; there were no murmurs. The lungs were clear.

Pretreatment Laboratory Data. (See table 2.) The urine and blood were normal. The electrocardiographic tracings were consistent with an old anteroseptal myocardial infarction. On x-ray examination, the heart was moderately enlarged to the left.

Post-treatment Course. On May 13, 1948, the patient received 25.5 mc. of I^{131} (table 1). Nine weeks after I^{131} the serum cholesterol was 427 mg. per cent and the basal metabolic rate was −29 per cent. The patient noted a diminution of night attacks and required no nitroglycerine in contrast to her previous state when she took three to four daily. During August, 1948, three months after I^{131}, frank myxedema occurred. On gradually increasing doses of thyroid from 12 to 36 mg. daily, the troublesome symptoms of myxedema cleared; angina pectoris recurred to approximately the pretreatment severity. However, she no longer had night attacks.

Comment: A 59 year old woman with hypertension and incapacitating angina pectoris of three years duration, was treated with one dose of I^{131}. Myxedema was induced with significant improvement in angina pectoris but with the thyroid dosage necessary to relieve discomfort, angina pectoris relapsed to pretreatment severity. There have been no nocturnal attacks, and she suffers no disability from the hypometabolic state. We do not consider the result worthwhile.

Case 13.—Arteriosclerotic heart disease with angina pectoris of six years' duration. Induction of myxedema by two doses of I^{131} with some relief of angina pectoris but with uncomfortable symptoms of myxedema. Result not considered worthwhile.

Pretreatment History. M. S., a 61 year old white male, B.I.H. #99719, received 42.5 mc. of I^{131} on July 15, 1948. Six years before I^{131}, the patient first experienced angina pectoris accompanied by dyspnea and relieved by rest. Attacks were precipitated by walking two blocks on the level or one flight of stairs, lasted eight to ten minutes, unrelieved by nitroglycerine.

Pretreatment Physical Examination. The patient appeared chronically ill. The thyroid was not palpable. The heart was not enlarged, the rhythm was regular, the sounds of distant quality. The lungs were clear. The blood pressure was 100/60.

Pretreatment Laboratory Data. (See table 2.) The blood and urine were normal. X-ray examination revealed marked left ventricular enlargement. The electrocardiogram was abnormal, the pattern not diagnostic. Following a tracer dose of I^{131} the urinary excretion was 77 per cent.

Post-treatment Course. On July 15, 1948, the patient received 42.5 mc. of I^{131}; the seventy-two-hour urinary excretion was 71 per cent. Two weeks later, moderate thyroiditis was accompanied by increased anginal pain and dyspnea despite less exertion. Twenty-five nitroglycerine tablets per week were used in contrast to only 5 to 6 per week in the preceding period. The exercise tolerance test was eleven to thirteen trips. The thyroiditis subsided during the next two weeks. Nine weeks after I^{131}, mild hypothyroidism was associated with slight improvement in the angina pectoris; the attacks were shorter, not as severe and required more exertion to precipitate them. The exercise tolerance tests averaged twenty-seven trips, compared to eighteen trips before I^{131}. The basal metabolic rate was −15 per cent and the serum cholesterol 320 mg. per cent. It was thought desirable to lower the metabolism even more in an attempt to effect additional improvement. Therefore, on November 10, 1948 he received 56 mc. I^{131} (table 1). The basal metabolic rate decreased to −24 per cent and the serum cholesterol rose to 400 mg. per cent. Improvement in angina pectoris was maintained but not augmented. On gradually increasing doses of thyroid from 18 mg. to 60 mg. daily, some improvement in the symptoms of myxedema occurred. The frequency and severity of angina pectoris was slightly less than before I^{131}.

Comment: A 61 year old man with angina pectoris

of six years' duration received two doses of I^{131}. Hypometabolism and some concomitant improvement in angina pectoris followed. The exercise tolerance test increased from eighteen to twenty-seven trips. A second dose of I^{131} was administered, and myxedema was induced. On increasing doses of thyroid to 60 mg. daily, there was some improvement in the symptoms of myxedema. He was able to walk three to four blocks without developing angina (compared to two blocks before I^{131}) and felt that there was improvement. However, in view of the fact that improvement was not marked and that he still complains of some symptoms of hypometabolism, we believe the result in this case is not worthwhile.

Case 14.—Marked systolic arterial hypertension. Congestive heart failure for five years. Multiple episodes of acute pulmonary edema. Mild angina pectoris. Myxedema induced by one dose of I^{131}. No further cardiovascular symptomatology. A striking therapeutic result.

Pretreatment History. R. F, a 59 year old housewife, B.I.H. #72053A, received 25.5 mc. of I^{131} on April 2, 1948. Twenty-four years before, acute tonsillitis was followed by migratory joint pains. Hypertension was first noted seven years before I^{131}. Five years before treatment, she was hospitalized because of increasing dyspnea, orthopnea, substernal oppression, weakness, and weight loss of three month's duration. The diagnoses were hypertension, hypertensive heart disease, congestive heart failure, and thyrotoxicosis. The patient was treated with digitalis, low-salt diet and potassium iodide with incomplete relief. Treatment with thiouracil was followed by icterus, pruritis and diarrhea; biopsy of the liver revealed acute bile stasis; slow recovery followed omission of the drug.

Four years before I^{131} treatment, dyspnea, orthopnea, weakness and weight loss required a fourth hospital admission. Hemithyroidectomy was performed. The recurrent laryngeal nerve was cut and right cord paralysis resulted.

Potassium iodide was administered and continued, but twenty months before I^{131} treatment, readmission was necessary because of acute pulmonary edema. Following recovery, three basal metabolic rate determinations were ±0 per cent. Eight months before I^{131} treatment, potassium iodide was omitted. Two months before I^{131}, she noted marked dyspnea on slight exertion and anterior chest pain radiating to the left arm on moderate exertion, often relieved by nitroglycerine. During the two months before I^{131}, she also had had three or four episodes of acute pulmonary edema. Despite markedly restricted activity, digitalis, low salt diet and xanthines, symptoms continued.

Pretreatment Physical Examination. The patient was dyspneic; the neck veins were distended; blood pressure was 230/90. There was no tremor or tachycardia; basal pulse rate was regular, 62 to 66. The heart was markedly enlarged to the left; a basal systolic but no diastolic murmur was heard. There was slight peripheral edema.

Pretreatment Laboratory Examinations. (See table 3.) The blood, urine and stool were normal. Nonprotein nitrogen was 39 mg. per cent; total protein was 6.5 grams per cent. On x-ray examination, the heart was enlarged and the lung markings were increased. The electrocardiogram was consistent with left ventricular hypertrophy.

Post-treatment Course. On April 2, 1948, the patient received 25.5 mc. of I^{131} (table 1). Eleven weeks after treatment, myxedema was clinically obvious. The basal metabolic rate was —20 per cent, and 12 mg. of thyroid daily was prescribed. The patient noted definite decrease in dyspnea, no cough, no ankle swelling or orthopnea. She slept on one pillow. She had no further episodes of acute pulmonary edema, paroxysmal nocturnal dyspnea or any chest pain. Weakness and fatigability were not relieved by amphetamine sulphate. Improvement had been so striking and the decrease in metabolic rate so great that it was believed the thyroid dosage could be increased without precipitating congestive failure or acute pulmonary edema. Accordingly, the dose of thyroid was increased gradually to 60 mg., and subsequently to 100 mg. daily (table 3); ethinyl estradiol, 0.05 mg. daily, was also administered. The patient observed a sense of wellbeing with decreased nervousness and fatigability. The previous cardiovascular improvement has been sustained.

Comment: This 59 year old patient with a previous history of thyrotoxicosis received I^{131} for the treatment of congestive heart failure, recurrent acute pulmonary edema, paroxysmal nocturnal dyspnea and mild angina pectoris secondary to hypertensive heart disease. She had been observed in the endocrine and cardiac clinics during the five years before I^{131} treatment. At the time of I^{131} therapy there was some difference of opinion as to whether residual thyrotoxicosis was present; it was the consensus, based on the absence of symptoms and signs of thyrotoxicosis and the normal basal heart rate, that the patient was euthyroid, the increase in metabolic rate and low I^{131} excretion being attributed to arterial hypertension and congestive failure. Eleven weeks after 25.5 mc. I^{131}, myxedema was present. Thereafter, she had no acute pulmonary edema, paroxysmal nocturnal dyspnea, no angina pectoris and no symptoms of congestive failure. Fatigability and nervousness decreased with thyroid 100 mg. and ethinyl estradiol 0.05 mg. daily. The absence of cardiovascular symptoms has continued. The therapeutic result was striking.

TABLE 3.—*Summary of Results in Five Patients with Congestive Heart Failure*

Case, Initials, Sex, Age	Additional Diagnoses	Duration of Decompensation	Before and Months After I^{131} Therapy	Basal Metabolic Rate	Serum Cholesterol	Arm to Tongue Circulation Time	Vital Capacity	Venous Pressure	Dyspnea	Other Signs and Symptoms	Comment	Therapeutic Result*
		Years		%	*mg./100 cc.*	*sec.*	*cc.*	*mm. H_2O*				
14. R. F. F, 59	Art. hypertension, mild angina pectoris, previous thyrotoxicosis	5	Before	+20	213	13	1700	130	Yes	Mild angina pectoris, multiple episodes of acute pulmonary edema. Slight peripheral edema.		++++
			15	−15	360	16	1825	100	None	Complete disappearance of above	Thyroid 90 mg.	
15. M. G. M, 44	Hypertensive and arteriosclerotic h.d. 2 prior myocardial infarcts, chronic renal disease	1.5	Before	+0	255	35	2200	260	Yes	Cyanosis, ascites, orthopnea 6–8 pillows, ++ peripheral edema, rales, liver enlarged 5 fingers		++++
			10	Not feasible	500	30	3650	65	None	Complete disappearance of above	Thyroid 6 mg.	
16. E.M. F, 46	Rheum. heart disease, mitral and aortic sten. and insuff.	7	Before	+5	220	42	1700	140	Yes	Frequent parox. noct. dysp.; pleural effusion; ascites; cyanosis		++
			24	−22	400	42	1750	100	Yes	Diminished frequency of noct. dysp.; no pleural effusion; no cyanosis; slight ascites	Thyroid 6–12 mg. daily for 18 mos. Marked improvement for more than a year	
17. E. D. F, 47	Rheum. heart disease, mitral sten. and insuff.	17	Before	−4	210	19	1350	230 to 300	Yes	Pulm. emboli; parox. noct. dysp.; probable rheumatoid arthritis; slight peripheral edema		0
			17	−27	350	—	1200	120	Less	No peripheral edema	Thyroid 15 mg. No dramatic change in cong. failure	
18. N. A. F, 43	Rheum. heart disease, mitral and aortic sten. and insuff., multiple pulmonary emboli.	6	Before	+7	205 to 280	29	2000	140	Yes	Occ. parox. noct. dysp.		0
			9	−15	250 to 350	—	1500	170	Yes	No change	Thyroid 12 mg.	

* ++++ striking; +++ excellent; ++ good; + fair; 0 not worthwhile.

Case 15.—Hypertensive and arteriosclerotic heart disease. Two previous attacks of acute myocardial infarction seven and five years before I^{131}. Chronic renal disease with one remaining kidney. Chronic severe congestive heart failure. Auricular fibrillation. Myxedema induced by two doses of I^{131} with marked improvement in all manifestations of congestive failure. A striking therapeutic result.

Pretreatment History. A male, M. G., 44 years of age, a former automobile mechanic, B.I.H. #M1759, received 27 mc. I^{131} on October 12, 1948. Hypertension had been noted nine years before treatment. He suffered an attack of acute posterior myocardial infarction seven years before treatment. Three days after getting out of bed a second attack, lasting one hour, occurred. Two years later a similar episode was treated by some weeks of bed rest following the taking of an electrocardiogram. The patient then changed to a more sedentary type of work and was fairly well until one and one-half years before I^{131} therapy, when he noted the onset of ankle edema. The blood pressure was 230/120. A nonfunctioning kidney was demonstrated and a left nephrectomy was performed. The blood pressure was said to have dropped to 114/70. Five months before entry he noted recurrence of ankle edema, increased weight and dyspnea. Despite a low-salt diet, digitoxin and mercurial diuretics, the dyspnea, orthopnea and intermittent edema became worse and he was hospitalized. On vigorous treatment with bed rest, low salt diet, a period on a rice diet, digitoxin, supplementary vitamins and frequent injections of mercurial diuretics as well as thoracenteses, the patient improved only slowly during seven weeks of hospitalization. At the time of maximum improvement, however, there was 1+ pitting of the ankles and 2+ pitting over the sacrum.

Pretreatment Physical Examination. The patient was dyspneic, orthopneic and slightly cyanotic. The blood pressure was 130/80. The neck veins were distended. The thyroid was barely palpable and non-nodular. There were dullness and diminished breath sounds at the right lung base posteriorly with moist rales at both bases. The heart was enlarged to the anterior axillary line; the rhythm grossly irregular. There was a Grade I apical systolic murmur. The abdomen was protuberant. The liver was firm, nontender and palpable, five fingers below the right costal margin. The splenic tip was palpable. Pitting edema over the sacrum was 2+, and over the ankles, 1+.

Pretreatment Laboratory Examinations. (See table 3.) The urine specific gravity was 1.019, plus 2 to plus 4 albumin; the sediment showed 1 to 10 white cells, occasional erythrocytes and fine granular casts. Blood was normal. The nonprotein nitrogen was 54 mg. per cent. On x-ray examination, the heart was dilated to the left and the right. Electrocardiograms showed auricular fibrillation and evidence of old posterolateral infarction and left ventricular hypertrophy. The seventy-two-hour urinary excretion of a tracer dose of I^{131} was 29 per cent, evidently due to the presence of severe congestive failure.

Post-treatment Course. On October 12 and October 23, 1948 the patient received 27 mc. and 30.5 mc. I^{131}, respectively (table 1). In the immediate post-treatment period, he continued to show 4 to 5 pillow orthopnea, dyspnea, markedly distended neck veins, auricular fibrillation with a pulse deficit of approximately 60, flatness and diminished breath sounds at the right base, the liver edge at the level of the umbilicus, +++ edema of the left leg, and + edema of the right leg. The dose of digitalis was increased, ammonium chloride and mercurial diuretics were again given and some improvement was noted. During the first two months after I^{131} treatment, the cholesterol decreased slightly from 278 to about 238 mg. per cent, and then began to rise, reaching and remaining at a level of 500 mg. per cent. The patient's face became puffy, his hands cool and dry, but he experienced no symptoms of hypothyroidism. During this period of hypometabolism he demonstrated progressive improvement.

At the present time, six months after induction of myxedema, he is able to undertake considerable increased activity, including doing some carpentry and considerable walking, without developing dyspnea. Orthopnea has decreased from 6 to 8 pillows and is no longer present. He sleeps on one pillow. The patient states that he has not felt this well in the last two years. Venous distention has diminished and there is no peripheral edema. Lungs are clear to percussion and auscultation. Ascites, present at the time of treatment, did not recur after one paracentesis. Neither spleen nor liver is now palpable. The transverse diameter of the heart, as measured by physical examination and as checked by x-ray examination, has diminished 4.8 cm. The electrocardiogram is unchanged. Venous pressure is 65 mm. of water, vital capacity is 3650 cc. (2350 complemental air and 1300 supplemental air), and the arm-to-tongue circulation time is thirty seconds. The nonprotein nitrogen has remained approximately 60 mg. per cent.

Comment: A 44 year old male with hypertensive and arteriosclerotic heart disease, two previous myocardial infarctions and severe intractable congestive failure, complicated by chronic renal disease in the one remaining kidney, was treated with two doses of I^{131}. Myxedema was induced and concomitantly there was striking improvement in congestive failure, despite greatly increased activity. There was decreased dyspnea, no orthopnea, no edema. The vital capacity

* ++++ striking; +++ excellent; ++ good; + fair; 0 not worthwhile.

increased from 2200 to 3650 cc. and the venous pressure decreased from 260 to 60 mm. He has experienced no discomfort from hypometabolism and at present is on 6 mg. thyroid daily. A striking therapeutic result.

Case 16.—Rheumatic heart disease with auricular fibrillation, mitral and aortic stenosis and insufficiency, chronic congestive heart failure for seven years. Severe exacerbation with general anasarca one year before I^{131} treatment, recurrent paroxysmal nocturnal dyspnea. Myxedema induced with two doses of I^{131}. A good therapeutic result.

Pretreatment History. E. M., a 46 year old housewife, B.I.H. #M177, received 8.5 mc. I^{131} on July 5, 1947. She entered the hospital in 1941 because of progressive ankle edema, dyspnea and orthopnea during the previous year. She had had chorea at the age of 10. Physical examination revealed marked cardiac enlargement, mitral and aortic stenosis and insufficiency, auricular fibrillation, congestion of the lungs and liver, ankle edema and orthopnea. She improved after one week in the hospital. In 1942, symptoms and signs of thyrotoxicosis appeared; the basal metabolic rate was approximately plus 33 per cent. A maximal subtotal thyroidectomy was done in 1943. Myxedema followed and the signs and symptoms of congestive heart failure markedly improved and she returned to work. Thyroid extract, 65 mg., was administered daily until January 1947, when for the fifth time the patient entered the hospital with orthopnea, pleural effusion, ascites, and peripheral edema. Thyroid medication was omitted. Despite adequate digitalization, frequent mercurial diuretics, and salt restriction, little improvement resulted. Following discharge from the hospital, the above signs and symptoms became progressively worse, paroxysmal nocturnal dyspnea appeared, and she re-entered on June 14, 1947. Only slight improvement resulted from the above regime of treatment.

Pretreatment Physical Examination. The patient was dyspneic, orthopneic, and deeply cyanotic. There was marked engorgement of the neck veins. The blood pressure was 160/80. The heart was greatly enlarged, and the characteristic murmurs of aortic and mitral stenosis and insufficiency were audible. Auricular fibrillation and, at times, a bigeminal rhythm were present. The firm, non-tender edge of the liver was felt four fingersbreadth below the right costal margin. Ascites was present. There was 3+ edema of the lower legs and slight edema over the sacrum.

Pretreatment Laboratory Data. (See table 3.) The urine specific gravity was 1.010 with intermittent albuminuria. The nonprotein nitrogen was 40 mg. per cent. The blood was normal. The electrocardiogram revealed auricular fibrillation, ventricular premature beats and left ventricular hypertrophy. By x-ray examination the cardiac transverse diameter was 18.3 cm. with marked left and right dilatation.

Post-treatment Clinical Course. On July 5, 1947, 8.5 mc. of I^{131} were administered (table 1). Approximately ten weeks later the basal metabolic rate was −14 per cent and the serum cholesterol 400 mg. per cent. On November 1, 1947 24 mc. of I^{131} were administered (table 1). A tracer study on December 4, 1947 showed 84 per cent excretion in three days. On December 10, 1947, six weeks after the second dose, the basal metabolic rate was −26 per cent and the serum cholesterol was 440 mg. per cent. Clinical evidences of myxedema were present. Her cardiac status improved. She was able to sleep flat in bed and undertake considerably more effort without dyspnea. Peripheral edema reaccumulated more slowly and, therefore, mercurial diuretics were required less frequently. Thyroid, 6 mg. per day, mitigated the symptoms of myxedema and enabled the patient to maintain clinical improvement. In the following nineteen months, the patient has been maintained in a hypometabolic state (table 3). She has had two additional hospital admissions, four months and twelve months after the induction of hypometabolism, for further regulation of congestive failure. The first was occasioned by cessation of mercurial diuretics, because of temporary intolerance to these compounds, and the second was precipitated by a period in which she was refractory to mercurial compounds. This, too, was temporary. At all other times the patient was ambulatory, able to do her own housework and run her own home, leading a restricted but otherwise normal existence. During recent hot humid weather immediately preceding an injection of a mercurial diuretic, she has had intermittent paroxysmal dyspnea. There is some but less dyspnea on exertion particularly on bending, orthopnea requiring the use of two pillows and swelling of the ankles. She has been on a regimen of digitoxin, ammonium chloride, and biweekly injections of mercurial diuretics. On thyroid 12 mg. daily, she has had no symptoms referable to her hypometabolism.

Physical examination reveals signs of moderate hypometabolism. The lungs are clear. The liver is palpable and occasionally tender, two to four fingersbreadth below the right costal margin. There is little sacral edema but marked edema of the ankles.

Comment.: This 46 year old woman with a past history of rheumatic heart disease and chronic congestive failure for seven years was completely incapacitated at the time of the inception of hypometabolism nineteen months ago. Congestive failure previously uncontrolled was markedly improved in that dyspnea, orthopnea, paroxysmal nocturnal dyspnea were ameliorated with the occurrence of hypometabolism following

I^{131}. She has been able to do her own housework, visit friends, and lead a generally more active though still restricted regimen. At the present time, two years after I^{131} treatment, there has been an exacerbation of the symptoms of congestive heart failure, and paroxysmal nocturnal dyspnea has been troublesome. The period of nineteen months of definite clinical improvement despite a more active life constitutes a good therapeutic result.

Case 17.—Rheumatic heart disease with auricular fibrillation, mitral stenosis and insufficiency. Recurrent congestive failure, requiring seventeen hospital admissions in seventeen years. Multiple attacks of pulmonary embolism, paroxysmal nocturnal dyspnea. Myxedema induced by a single dose of 27 mc. of I^{131}. Congestive failure improved after treatment, but the change could be due to concomitant improvement in associated disease, probably rheumatoid arthritis and erythema nodosum, rendering estimate of therapeutic effect of I^{131} equivocal.

Pretreatment History. E. D., 47 year old receptionist, B.I.H. #M2717, received 27 mc. of I^{131} on February 12, 1948. Seventeen years before treatment, rheumatic heart disease with mitral stenosis and insufficiency was diagnosed. In the nine years before her first entry to the Beth Israel Hospital, while under the care of Dr. Samuel L. Gargill, she was hospitalized elsewhere twelve times because of severe dyspnea, orthopnea, fatigue, chest pain, cough and ankle swelling. When admitted to the Beth Israel Hospital, eight years before I^{131} treatment, congestive failure, pulmonary edema, mitral stenosis and insufficiency, paroxysmal auricular fibrillation and paroxysmal nocturnal dyspnea were noted.

Seventeen months before I^{131}, a second admission, because of an acute upper respiratory infection, chronic congestive heart failure with auricular fibrillation, was complicated by phlebitis and pulmonary infarction. Early in 1948, repair of an inguinal hernia was complicated by pulmonary infarction. Throughout this pretreatment period, despite the presence of exertional dyspnea, four-pillow orthopnea, palpitation and edema of the legs, the patient continued to work as receptionist in a department store. Therapy consisted of digitoxin, low salt diet and occasional injections of mercurial diuretics.

Pretreatment Physical Examination: The patient was dyspneic and orthopneic. The heart was markedly enlarged and showed murmurs characteristic of mitral stenosis and insufficiency; the rhythm was grossly irregular; the rate 76. There was dullness at the right lung base posteriorly, with inconstant rales. A tender liver edge palpable four to five fingersbreadth below the right costal margin and minimal peripheral edema were noted.

Pretreatment Laboratory Examinations. (See table 3.) The blood, urine and stool were normal. Serology was negative. X-ray examination revealed a markedly enlarged heart, increased hilar shadows and markings, and small amount of fluid in the right costophrenic angle. The electrocardiogram revealed auricular fibrillation.

Post-treatment Course. On February 12, 1948, she received 27 mc. of I^{131} (table 1). The post-I^{131} course was complicated by the occurrence of thrush with a severe sore throat, purulent sinusitis, leg and joint pain and erythema nodosum and, later, acute cholecystitis and cholelithiasis. Seven weeks after I^{131}, the basal metabolic rate was −20 per cent. The excretion of successive tracer doses of I^{131} rose from 42 to 87 per cent. There was no evident change in the cardiovascular status. Four months after I^{131}, two months after the onset of myxedema, the patient noticed a decrease in exertional dyspnea and fewer episodes of paroxysmal nocturnal dyspnea. This improvement was temporary.

In the late spring of 1949, fifteen months after treatment, the patient began to improve with some remission of the joint symptoms, decrease in dyspnea and less frequent paroxysmal nocturnal dyspnea. In June 1949, acute cholecystitis and cholelithiasis required cholecystectomy. The patient withstood operation well and returned to work in four weeks.

Comment: This patient, with a seventeen-year history of rheumatic heart disease and recurrent congestive heart failure, received one dose of 27 mc. of I^{131}. It has been extremely difficult to evaluate the effect of the hypometabolic state in this patient, owing to the overlay of psychogenic factors and the continued presence of stiff, swollen and painful joints of the hands and feet, tender, blotchy, erythematous areas and exquisite tenderness of the lower extremities. There is less dyspnea and more infrequent paroxysmal nocturnal dyspnea. Orthopnea and chest pain persist. The vital capacity is unchanged. The venous pressure is 120 mm. of water as compared to 230 to 300 mm. prior to treatment. The basal metabolic rate is −27 per cent. The serum cholesterol is 350 mg. per cent. There are no symptoms referable to the hypometabolic state. She has continued to work and has been maintained on a regimen of desiccated thyroid 15 mg., digitoxin 0.1 mg., vitamins and intermittent injections of mercurial diuretics. While her cardiac condition has unquestionably improved, this cannot be confidently attributed to I^{131} because of concomitant improvement in the arthritis.

Case 18.—Rheumatic heart disease, mitral stenosis and insufficiency, aortic stenosis and

insufficiency, dyspnea on exertion for twenty years, auricular fibrillation for fifteen years, progressive congestive heart failure for six years with two admissions in the three months before treatment for marked congestive heart failure despite optimal therapy. Myxedema induced with one dose of I^{131}. Temporary but no lasting worthwhile improvement of congestive failure.

Pretreatment History. N. A., a 43 year old woman, B.I.H. #71514, received 39 mc. I^{131} on November 9, 1948. Twenty-five years previously polyarthritis occurred and there was intermittent recurrence during the next ten years. Twenty-one years ago she noted dyspnea on marked exertion with occasional ankle edema, and for the past fifteen years irregularity of the pulse. Twelve years prior to I^{131} treatment, acute paroxysmal dyspnea was experienced, and the diagnosis of rheumatic heart disease was made. Six years ago exacerbation of rheumatic fever, and again later that same year, mild congestive failure subsequent to a respiratory infection required hospitalization. She was subsequently followed in the Cardiac Clinic, and maintained on digitalis and ammonium chloride. She had moderate dyspnea, orthopnea, occasional paroxysmal nocturnal dyspnea and mild ankle swelling. Three years ago she was hospitalized for increasingly severe congestive failure and hydrothorax and again three months before treatment because of congestive heart failure, polycythemia vera and multiple cerebral episodes with transient hemiparesis and aphasia.

Following discharge she experienced episodes of paroxysmal dyspnea, severe orthopnea, suffered marked dyspnea on minimal effort and gained 16 pounds despite a salt-free diet, digitoxin and a weekly injection of a mercurial diuretic. She was only barely able to do light housework. One month before treatment she was again admitted to the hospital with severe congestive failure, accompanied by persistent abdominal swelling. An enlarged liver, abdominal ascites, right hydrothorax, evidence of hepatic insufficiency with serum bilirubin of 0.8 mg. per cent, icteric index of 13 to 19 and sulphobromophthalein sodium retention of 26 per cent in forty-five minutes were noted. The patient responded to vigorous treatment with bed rest, diuretics and digitalis.

Pretreatment Physical Examination. The patient was mildly dyspneic, cyanotic and orthopneic. The thyroid was palpable. The lungs were clear. The heart was markedly enlarged to the left. The rhythm was grossly irregular, and with bigeminy, trigeminy and quadrigeminy. The characteristic signs of advanced mitral stenosis and insufficiency were heard. The nontender liver was palpable three to four fingersbreadth below the right costal margin. There was ascites and no ankle edema.

Pretreatment Laboratory Examinations. (See table 3.) Most urine specimens revealed a specific gravity of 1.017 with 2 to 3 plus albumin, 10 to 12 white blood cells and occasional red blood cells. The hemoglobin was 13.9 grams, red blood count 4.5 million, white blood count 6,850 with a normal differential count. The nonprotein nitrogen was 38 mg. per cent, the icteric index 13–19, total protein 7.8 Gm. per cent; normal albumin/globulin ratio. On x-ray examination the heart was markedly enlarged to the right and to the left, the transverse diameter being 17 cm.

The electrocardiogram showed auricular fibrillation, multiple ventricular extrasystoles, right axis deviation and was consistent with left and right ventricular hypertrophy. In the seventy-two hours following a tracer dose of I^{131}, 58 per cent was excreted in the urine.

Post-treatment Clinical Course. On November 9 1948, 39 mc. of I^{131} were administered (table 1). Four weeks later, she suffered an embolus to the left popliteal artery and left kidney. She recovered gradually without sequelae.

Ten weeks after I^{131}, the basal metabolic rate was −25 per cent and there was slight improvement in congestive failure, manifested by some decrease in dyspnea and orthopnea. In the following weeks further improvement occurred. She was able to undertake more housework and could sleep almost flat, had no cough and much less abdominal swelling than previously. At this time she achieved the peak of her improvement. She stated that her breathing had not been so good in two years. With the administration of thyroid, 20 mg. daily, the basal metabolic rate gradually rose to −15 per cent and congestive failure recurred (table 3); compensation was maintained only by the use of weekly injections of mercurial diuretics. She continued to show an enlarged liver, right pleural effusion and evidence of ascites. The rhythm continued to be irregular with bigeminy and trigeminy.

Comment: A 43 year old woman with rheumatic heart disease, progressive congestive heart failure, complicated by multiple embolic phenomena, and probably cardiac cirrhosis was treated with one dose of I^{131}. Myxedema was induced and was associated with temporary clinical improvement. At the present time, six months after induction of myxedema, congestive heart failure is controlled with difficulty on a rigid medical regimen, and weekly injection of diuretics. On 12 mg. of thyroid daily, she suffers no discomfort from hypometabolism. Her cardiac condition is approximately the same as before I^{131} and the therapeutic result is not considered worthwhile.

Discussion of Results

The accurate evaluation of every clinical therapeutic measure is beset by the possibly

favorable effect of suggestion and spontaneous improvement due to changes in the natural history of the condition. Throughout this investigation we have tried to reduce such errors to a minimum. Practically all patients were treated on an ambulatory basis, obviating the possible effect of prolonged bed rest and hospitalization. Following administration of I^{131}, hypothyroidism appeared only after five weeks to five months, and could not be anticipated by either the patient or the observers. It was particularly impressive to have the patient report, after receiving I^{131}, that for the first time in months or years he felt definitely improved, and then to find definite improvement on physical examination. Concomitantly, the laboratory reports of the basal metabolic rate measurements and serum cholesterol determinations indicated the inception of hypothyroidism (fig. 1, Case 3). Conversely, some patients, during the period in which they gave evidences of thyroiditis as manifested by pain and tenderness with increased heat over the thyroid area, noted their condition was definitely worse. In some of these individuals the basal metabolic rate was slightly elevated (figs. 1 and 2, Cases 3 and 5). We have observed in such instances an elevation of the serum protein-bound iodine measurement. Several patients during this time also exhibited slight tachycardia and increased nervousness and sweating indicative of mild hyperthyroidism. As clinical improvement became evident, the degree of improvement generally was proportional to the degree of hypothyroidism. This correspondence between metabolic levels and clinical status was manifested in twenty-six episodes in the 18 patients.

The observed relation between the metabolic rate and clinical improvement is a clear verification of the rationale of this procedure which has been elucidated in previous communications,[1, 2, 28, 29] and, therefore, will be described only briefly. Circulation and metabolism are two closely related fundamental characteristics for, clearly, metabolic activity of the tissues would be impossible without adequate blood supply. The normal metabolic level of the body is maintained by the normal thyroid. With decreased function of the thyroid, the metabolic level is decreased until, in the absence of thyroid function, the basal metabolic rate is approximately 40 per cent below normal. At these levels the cardiac work, as indicated by the diminished output and the slower speed of blood flow,[1, 30] is decreased; the decrease in circulation is, indeed, even more than the metabolic rate would indicate, for the arteriovenous oxygen difference is widened. It was thought, therefore, that the diseased heart, while unable to meet the demands of normal metabolic and circulatory requirements, nevertheless might be able to meet the reduced needs in hypothyroidism.

Clinically, it has long been known that subtotal thyroidectomy in thyrocardiac patients usually accomplishes permanent lowering of the basal metabolic rate from abnormally high levels to a normal level, with coincident improvement in angina pectoris and congestive failure as the demands on the heart are lessened.[31-33] Conversely, when thyroid is administered to patients with spontaneous myxedema, angina pectoris[34-36] and the signs and symptoms of congestive failure[36-38] not infrequently develop because of the increased demands on the heart.[39-41] It is well recognized that exercise, emotion and other factors which increase cardiac work tend to aggravate angina pectoris and congestive failure. The enforcement of diminished activity or complete bed rest benefits patients by reducing the demands on the heart. The use of sedatives and the action of digitalis in reducing the ventricular rate in auricular fibrillation have a similar effect.

The induction of hypothyroidism for the treatment of angina pectoris and congestive failure is an extension of this therapeutic principle. In lessening the demands on the heart in patients with intractable heart disease by purposefully inducing myxedema, a diminution in cardiac work is accomplished. Since the heart in hypothyroidism performs less work and starts at a lower level of oxygen consumption, it can withstand a greater increment of work before reaching the upper limit of its work capacity. This upper limit of work capacity in patients with congestive failure is imposed by the presence of valvular disease, hypertension, or injury because of rheumatic myocarditis or prior myocardial infarction. In angina pectoris,

many of these factors, as well as the limitation of blood supply by the relatively fixed arteriosclerotic coronary vessels, are operative; the coronary circulation cannot increase in accordance with the increased needs of the heart. Relative anoxemia results, and angina pectoris occurs.

The hypothyroid state also possibly exerts a favorable effect in several other directions. When patients are frankly myxedematous with basal metabolic rates of −30 to −40 per cent they are often irritable and nervous but, on receiving small doses of thyroid to maintain them at a level of −15 to −25 per cent, they are frequently more placid and even-tempered emotionally than before treatment, though mentally as acute as formerly. In an occasional patient, such as J. K. (Case 3), this factor may be significant; the patient stating that all his life prior to treatment he was prone "to fly off the handle whereas now I am more even-tempered." Accordingly, after the induction of myxedema, small doses of 6 to 100 milligrams of thyroid are administered daily to maintain all patients at a level, usually of −15 to −25 per cent, at which they experience the least discomfort from myxedema and the maximum relief from their cardiac symptoms.

The question naturally arises whether the increased emotional stability in some of our patients is due to a lessened sensitivity to epinephrine. Previous studies[42] of the effects of known concentrations of epinephrine administered intravenously before total thyroidectomy and at various metabolic levels after operation demonstrated that the response of blood pressure, cardiac rate, oxygen consumption and respiration remained unchanged as long as the basal metabolic rate was not lower than −30 per cent and the patient was free from the distressing symptoms of myxedema. At levels below that at which our patients are maintained, a decreased response of the blood pressure and the heart rate to epinephrine became manifest in some instances. These observations on the unaltered sensitivity to epinephrine at the metabolic levels maintained in our patients do not preclude the possibility, however, that a decreased secretion occurs in the hypothyroid state.

The Effect of Hypothyroidism on Angina Pectoris

Angina pectoris has been strikingly lessened or abolished in 8 of the 13 patients with intractable cardiac pain (table 2). The duration of angina pectoris in these 8 patients was from one to ten years and averaged three years, eight months. All of these patients had experienced cardiac pain on exertion and many had attacks on emotion; several had pain which came on at rest and even during sleep. The improvement has been particularly striking in five patients (Cases 1 to 5). These patients are able to undertake considerably more exertion than formerly with only occasional or no attacks of angina pectoris. Cases 1 and 2 are gainfully employed, whereas prior to treatment they had been completely incapacitated for years because of angina which was precipitated by the slightest effort. In the other 3 of the 8 patients, the result has been definitely worthwhile according to the appraisal by the patient and by us. In addition to the foregoing 8 patients, Case 14, incapacitated primarily because of congestive failure, also suffered angina pectoris on moderate exertion. With improvement in the congestive failure, angina pectoris no longer occurs.

In the remaining 5 of the 13 patients with angina pectoris, the therapeutic result has not been striking. In Case 9, angina pectoris was relieved for nine months but has since relapsed to pretreatment status. In the 4 patients (Cases 10, 11, 12 and 13) in whom the therapeutic result was not considered worthwhile, angina pectoris was either strikingly lessened or abolished when the patients exhibited the clinical and laboratory evidences of myxedema. It was impossible, however, to maintain these patients at such metabolic levels because of the discomfort of myxedema. When thyroid was administered to ameliorate the discomfort of myxedema, attacks of angina pectoris occurred with sufficient frequency and severity to make us consider the result not worthwhile. Some of these patients have been restored to their pretreatment euthyroid status by thyroid with return of their cardiac pain to its pretreatment characteristics.

The Effect of Hypothyroidism on Congestive Heart Failure, Paroxysmal Nocturnal Dyspnea and Pulmonary Edema

Five of the 18 patients were incapacitated primarily because of congestive heart failure (table 3). Three of the 5 patients (Cases 14, 15 and 16) showed worthwhile improvement; in the first 2 the improvement has been striking. The relief from dyspnea, attacks of pulmonary edema and paroxysmal nocturnal dyspnea has been associated with objective evidences of diminution (Case 16) or disappearance (Cases 14 and 15) of peripheral edema and of pulmonary congestion. In Patient 15, orthopnea is no longer present, ascites has remained absent, the liver is no longer palpable, cyanosis has disappeared and the vital capacity of the lungs has increased from 2200 cc. to 3650 cc. The patient is able to engage in useful activity for the first time in one and one-half years.

In the 2 patients in whom a worthwhile therapeutic effect could not be ascribed to I^{131} therapy, definite improvement of congestive failure occurred in one (Case 17) but this may have been due to improvement in the concomitant rheumatoid arthritis. In the other patient (Case 18), definite temporary improvement was evident for approximately one month followed by relapse to her pretreatment status consequent to small doses of thyroid.

In addition to these 5 patients, symptoms and signs of congestive failure were present in many of those incapacitated primarily because of angina pectoris. Congestive failure had been noted for ten years in Patient 4, for five years in Patient 6 with episodes of peripheral edema, pulmonary congestion, recurrent paroxysmal nocturnal dyspnea and orthopnea. Paroxysmal dyspnea and attacks of acute pulmonary edema had also occurred in Cases 2 and 3. In all of these patients the significant improvement in angina pectoris was associated with comparable improvement in the manifestations of congestive failure, the signs and symptoms being impressively relieved or entirely dissipated.

Effect on Associated Diseases

Diabetes mellitus was present in 2 patients (Cases 8 and 12). In one patient, the disease was mild and required no insulin; no change could be discerned after treatment. In the other patient, 56 units of protamine and 20 units of regular insulin were required daily before treatment, compared to 50 and 12 units after treatment; the control of glycosuria was better after treatment. While not as striking a reduction in insulin requirement as observed in some cases after total thyroidectomy, the amelioration of diabetes mellitus is in accordance with our previous experience.[43]

Advanced chronic nephritis was present in one patient (Case 15). The striking improvement in congestive failure in this patient was not followed by any striking change in the blood nonprotein nitrogen.

Changes in Objective Clinical Measurements after Induction of Hypothyroidism

The basal metabolic rate has been significantly lowered in every patient thus far treated. The decrease in metabolic rate has become evident five weeks to five months after treatment. In some instances, no effect has been noted after the initial dose of I^{131} and one or more additional doses were necessary. In most patients, a state of frank myxedema was permitted to become manifest before thyroid medication was administered, but in certain patients an optimal hypothyroid state has been induced and thyroid medication was not necessary. When patients are in marked myxedema, the discomfort not infrequently prevents attainment of a true basal state. Administration of small doses of thyroid makes them more comfortable and consequently in such patients one may occasionally witness an initial decrease in metabolic rate from higher levels to -25 per cent or -30 per cent when thyroid is administered.

The serum cholesterol measurements provide an invaluable guide in the estimation of the presence and degree of hypothyroidism.[44] They are of particular importance in those individuals, such as Cases 4, 8 and 15 in whom reliable basal metabolic measurements cannot be obtained. Definite increases in serum cholesterol, coincident with clinical improvement, were at times noted a week or two before a significant decrease in basal metabolic rate became manifest. This was observed particularly in patients

in whom some variation in metabolic rate determinations could not be obviated.

The velocity of blood flow also shows significant changes. Previous studies[1, 45] demonstrated that the speed of blood flow is slowed in myxedema. In the usual euthyroid patient with congestive failure, the blood flow is also slowed but becomes more rapid as compensation is regained. In accordance with these studies, we have observed that patients with angina pectoris but no congestive failure (Cases 3, 5, 7) showed a slowing in velocity of blood flow as hypothyroidism was induced. In patients with congestive failure who showed clinical improvement as hypothyroidism developed, two opposing influences were operative; the clinical improvement and regaining of compensation tend to cause an increased blood flow; the hypothyroidism, a decreased flow. Measurements of the arm to tongue circulation times under such circumstances represent the resultant of these two opposing influences. Thus in Case 15 there was an increased speed of blood flow because of the preponderant influence of striking clinical improvement, whereas in Case 16 the arm to tongue circulation remained approximately the same; the two opposing influences tending to offset each other. In Cases 14 and 17 the velocity of blood flow was decreased.

Arterial hypertension had been experienced by 7 patients (Cases 2, 6, 7, 10, 12, 14, 15). No effect on blood pressure levels was discerned.

The vital capacity of the lungs and its subdivisions underwent a decided increase in the one patient with striking improvement in whom the measurement was feasible (Case 15). In myxedema, the vital capacity of the lungs is abnormally low even in the absence of symptoms or signs of congestive failure.[45] In patients with improvement in congestive failure induced by hypothyroidism, vital capacity measurements are evidently the resultant of two opposing factors: (1) improvement in congestive failure tending to increase the vital capacity of the lungs and (2) development of the low metabolic rate of myxedema tending to lower the vital capacity of the lungs.

Exercise tolerance tests were considered hazardous in most of the patients with angina pectoris in whom attacks occurred on very slight exertion or even at rest and in whom episodes of paroxysmal dyspnea and acute pulmonary edema frequently had been observed. In Patient 1, the increased ability to undertake effort during the test was in accordance with his striking improvement manifest in daily activities; in Patient 9, the results of the exercise tolerance test were also in accordance with the clinical appraisal.

The Development of the Signs and Symptoms of Clinical Myxedema, Including Electrocardiographic and Heart Size Changes

After the administration of therapeutic doses of I^{131}, no discernible evidences of hypothyroidism were noted for five weeks to five months. In approximately one-third of the cases receiving single doses of 8.5 to 56 millicuries, tenderness and occasionally slight pain have been observed over the thyroid (table 1) persisting usually several days, but occasionally, seven or ten days. Concomitant with these manifestations of probable thyroiditis, slight elevations in the metabolic rate, slight tachycardia, elevation of the serum protein-bound iodine have been noted. With these evidences of mild hyperthyroidism, the symptoms and signs of angina pectoris sometimes became slightly but definitely worse during this brief period (Cases 3 and 5).

The first intimation of incipient hypothyroidism may consist of one or more of the following: rise in serum cholesterol, decreased basal metabolic rate, slight fullness or puffiness of the face, a report by the patient that the attacks of angina are milder or less frequent, improvement in the dyspnea of congestive failure or lessening of orthopnea.

During the next weeks or months the clinical evidences of myxedema become more definite. In a few patients, such as Case 15, an optimal level of hypometabolism is reached and maintained for a considerable period during which no thyroid medication or further I^{131} dosage is indicated.

Most patients experience discomfort at basal metabolic levels below -25 per cent but considerable individual variations have been ob-

served. Some patients tolerate levels as low as −23 per cent (Case 5) or −24 per cent (Case 3) without any significant discomfort; others must be maintained at relatively high levels such as −15 per cent (Case 14). Patients 1, 2, 3, 5 and 15 are maintained in the hypometabolic state with little or no discomfort, whereas others (Cases 11, 12 and 13) are uncomfortable at similarly decreased levels. The explanation of the considerable individual differences is not clear. The distress of myxedema which requires thyroid therapy includes the following: lethargy and sleepiness, stuffiness of the nose and ears, stiffness and ache of the muscles and joints, paresthesias, weakness of the legs, irritability and depression, puffiness of the eyes and face.

In each instance, thyroid dosage must be adjusted to maintain the patient at the lowest level at which he experiences the maximum relief from his cardiac disease and the minimum discomfort from myxedema. In certain patients (Cases 11, 12 and 13), this has not been possible, the patient showing little or no improvement over his pretreatment status when sufficient thyroid was administered to obviate the discomfort. In general, a pretreatment basal metabolic level of −10 per cent or higher permits a greater leeway.

Each of the present authors has been impressed with the fact that at comfortable levels of hypometabolism, usually −15 to −25 per cent, the patients are bright and alert rather than mentally lethargic.

The Question of "the Myxedema Heart"

As in previous studies, particular attention has been devoted to the appearance of evidence of the signs or symptoms of the so-called "myxedema heart." Observations of the heart in spontaneous myxedema[34, 46-52] demonstrated that (1) the cardiac silhouette on x-ray examination and the area of percussion dullness on physical examination are usually increased; (2) the voltage of the P and T waves and the QRS complex in the three standard leads is frequently diminished[53, 54] and the P-R interval is increased[52, 54]; and (3) cardiac contractions are less forceful.[51, 54] Opinions differ concerning the clinical significance of these alterations. Zondek[55, 56] and Fahr[57, 58] maintained that cardiac function is often impaired in patients with myxedema having such changes. Willius and Haines[59], Case[50] and Means, White and Krantz,[34] however, studied a total of three hundred patients with myxedema and concluded that heart function is rarely, if ever, impaired. From a review of the literature and a comprehensive study of 30 additional cases at the Massachusetts General Hospital, Lerman, Clark and Means[49] concluded that "myxedema heart" in the sense of heart failure occurs rarely, if at all—an opinion likewise expressed by Christian.[40, 60]

Our own observations are in accordance with the latter findings; an increased cardiac silhouette or area of percussion dullness, decreased voltage of the electrocardiogram and less forceful pulsations on fluoroscopy have been observed in some of our subjects. But "myxedema heart" in the sense of a condition aggravating or precipitating attacks of angina pectoris or congestive failure did not develop in our cardiac patients. On the contrary, with the appearance of such changes, striking clinical improvement has been witnessed. In some patients with congestive failure, the cardiac silhouette became smaller, the disappearance of the dilatation of the failing heart offsetting the effect of myxedema on the heart. We believe that the designation, "the heart in myxedema," is more accurate than the term "myxedema heart" as employed by Zondek[55, 56] and Fahr.[57, 58] A detailed report of our findings will be presented subsequently.

Hypercholesterolemia, Myxedema and Arteriosclerosis

The question naturally arises as to whether the hypercholesterolemia in hypothyroidism predisposes the patient to an increased progression of arteriosclerosis. Despite the common statement that arteriosclerosis is conspicuous in myxedema, the evidence is not conclusive.[61-63] In our own patients, the situation is, moreover, not strictly analagous to untreated or complete myxedema, since our patients are maintained at basal metabolic levels of −15 to −25 per cent and almost always receive small doses of thyroid.

In this connection we have reviewed the clinical course and postmortem findings of patients who survived three to eleven years following surgical total thyroidectomy and in whom hypometabolism with elevated cholesterol values was present. Cases with angina pectoris in the fifth decade or beyond shed no light on this question, for pathologic studies[64, 65] have clearly demonstrated that such patients have extensive coronary arteriosclerosis in the absence of myxedema. We have, therefore, studied the findings in the younger patients with rheumatic heart disease who survived one or more years after total thyroidectomy and in whom basal metabolic readings, hypercholesterolemia or clinical manifestations of hypothyroidism was evident. Only slight or minimal coronary arteriosclerosis would ordinarily be anticipated at death. If decided arteriosclerotic lesions were disclosed after total thyroidectomy, they might well be attributed to the hypercholesterolemia of hypothyroidism. In all 5 such patients who survived three to eleven years after total thyroidectomy in the hypothyroid state, careful postmortem studies by the Schlesinger technic[64] revealed, however, only minimal or no coronary arteriosclerosis. Similar findings were disclosed in 3 additional cases of the Peter Bent Brigham Hospital made available to us through the courtesy of Dr. George W. Thorn and Dr. Samuel A. Levine. In one ambulatory patient, aged 39, with rheumatic heart disease, mitral stenosis and insufficiency, sixteen years after surgical total thyroidectomy, x-ray studies by Dr. Felix G. Fleischner, Roentgenologist to the Beth Israel Hospital, failed to reveal any evidence of calcification of the leg vessels, of the abdominal or thoracic aorta, coronary artery calcification or other similar abnormalities.

The Relative Advantages and Disadvantages of I^{131} Therapy to Induce Hypothyroidism Compared to Total Thyroidectomy

The many advantages of inducing hypothyroidism by radioactive iodine rather than total thyroidectomy may be summarized as follows: Surgical interference with its inevitable mortality, pain and discomfort is obviated. Prolonged hospitalization is not necessary. Some of our patients have been studied in the hospital for brief periods to facilitate our research; others, however, have been treated wholly on an ambulatory basis. In the evaluation of therapeutic benefit, the possible effect of bed rest in hospital need not be considered after radioactive iodine therapy. Total thyroidectomy, like subtotal thyroidectomy, entails possible damage to the parathyroids and recurrent laryngeal nerves, and the possibility of aberrant or residual thyroid tissue not readily seen or removed at operation. Immediately following total thyroidectomy, amelioration or disappearance of the pain of angina pectoris was observed due to the severance of sensory nerve pathways.[66, 67] This early relief is not enjoyed after I^{131} therapy, but on the other hand, the therapeutic effect of hypothyroidism per se can be more accurately observed, uncomplicated by this early relief, by the period of hospital bed rest, and by the possible effect of suggestion. The irregular interval of five weeks to five months after I^{131} treatment, before hypothyroidism becomes evident, is an additional safeguard against the possible effect of suggestion. The time at which hypometabolism and clinical improvement occurs cannot be foretold by the patient or the physician; the clinical improvement, first noted by the patient and later found to be coincident to the inception of hypometabolism when the results of the serum cholesterol and basal metabolic determinations are made available, is consequently the more impressive.

In the doses needed to induce myxedema, radioactive iodine therapy is not attended by any symptoms of radiation sickness or any other serious discomfort; in approximately two-thirds of the patients receiving 8.5 to 42.5 millicuries as the first dose, local tenderness and slight pain on swallowing roughly equivalent to the discomfort of an acute, mild to moderate sore throat has been noted for several days and up to a week. More recently, we have administered two to four doses of approximately 20 millicuries each to obviate these symptoms.

In 1933, it was stated[28]: "It is hoped that ultimately operation will be unnecessary to produce a low metabolic rate. Many studies

have been made on antithyroidal substances, and comparatively recent reports give hope that the administration of such substances may cause lowering of the metabolic rate." Radioactive iodine fulfills this hope but possesses certain disadvantages. Its use entails highly specialized skills and extensive apparatus of considerable cost. Patients require observation for an extended period of weeks or months to determine whether additional doses are required to produce hypothyroidism. Studies regarding dosage schedules, uptake by the thyroid, and the determination of the roentgens delivered are in progress, however, and are expected to be helpful in the future clinical management of these patients.[68]

In general it may be stated that radioactive iodine therapy imposes no pain or discomfort except temporarily in the instances of thyroiditis noted above. If the patient cannot tolerate the hypothyroid state, it may always be abolished by appropriate doses of thyroid.

Comparison of Propylthiouracil with I^{131} Therapy in Euthyroid Cardiac Patients

The thiourea derivatives, including propylthiouracil, also have been used to attain the hypometabolism of total thyroidectomy by medical instead of surgical means. These drugs are readily available, comparatively inexpensive, and, like I^{131}, are administered by mouth. Unfortunately, however, hypothyroidism can be induced in only some patients. Moreover, to maintain hypothyroidism in the patients in which it is effective, administration of the drug must be continued for the remainder of the patient's life. At any time during such administration, dangerous drug reactions, including granulocytopenia, agranulocytosis and death, may suddenly occur.[69-75]

Selection of Patients

The criteria for the proper selection of patients can be established only after the results of this therapy have been observed by various investigators over a period of many years in numerous patients representing the various forms and degrees of severity of cardiovascular disease. Although the results in these 18 patients during the past two years are informative, the duration of hypothyroidism is too short and the number of cases too small to permit the deduction of final conclusions. It may be of value, however, to state our tentative opinion at the present time.

We believe this procedure should still be considered in the investigative stage and, therefore, should be reserved for those patients who in spite of all available therapeutic medical measures remain cardiac invalids. Before radioactive iodine is administered, the patient's condition should be improved to the fullest possible extent by prolonged and adequate treatment in order that the effect of I^{131} therapy may be evaluated as clearly and as accurately as possible.

Patients whose incapacity is due in significant measure to other conditions which will not be helped by the hypometabolic state and which may even be adversely affected should not be accepted for treatment. Included in this category are patients with emotional instability, particularly with depressions (see Cases 7, 10 and 17), patients with intermittent claudication of the legs (Case 11), patients with rheumatoid arthritis (Case 17) or active rheumatic fever, and patients prone to embolic phenomena which may dominate the clinical situation at any time (Case 18).

Patients with a rapidly progressive clinical course should not be treated. There is no reason to believe that the induction of hypothyroidism will retard the development of arteriosclerosis or impede the narrowing of the valvular orifices or retard active syphilitic aortitis. One should expect that although patients who show a rapidly progressive pretreatment clinical course may experience temporary and perhaps considerable improvement, they will probably succumb to the underlying disease process sooner than other patients with a less rapidly progressing condition. Patients with malignant hypertension and with syphilitic heart disease having a short but progressive history of failure are unfavorable candidates.

Since this form of treatment is based on a fall in metabolic rate and since most patients experience discomfort from myxedema at levels of -25 per cent or less, regardless of the pretreatment level, it is evident that patients with

initial basal metabolic rates of −15 per cent or less, can experience but relatively slight change before requiring thyroid. We have, therefore, with but one exception, not undertaken I^{131} therapy in any patient with initial metabolic levels below −15 per cent. The one patient (Case 10) who constitutes the exception was relieved of angina pectoris when the basal metabolic rate was −42 per cent but experienced no worthwhile improvement when maintained at −25 per cent, which was practically identical with that before treatment.

In general, our results with patients with angina pectoris have been more striking than in those with congestive failure. In angina pectoris one is dealing with a solitary symptom which, when relieved or abolished, frees the patient from disability. In patients with congestive failure one usually can anticipate only partial relief from disability. If bedridden continuously with congestive failure, they may enjoy freedom from failure when up and about. If congestive failure develops on only mild exertion, they may enjoy a moderate increase in activity. With such increased activity, relief of dyspnea, paroxysmal nocturnal dyspnea, pulmonary edema and diminished frequency or abolition of injections of mercurial diuretics may be observed.

It may be helpful to state our present concept of a favorable candidate for I^{131} therapy. The patient is between 40 and 60 years of age with angina pectoris due to coronary arteriosclerosis. He is alert, intelligent, cooperative, and emotionally stable. He has suffered from frequent attacks daily on slight to moderate exertion, such as walking short distances or a flight of stairs. He has night attacks, or attacks at rest or after meals, despite all available medical measures and despite curtailing his activities. Although his angina pectoris is severe, it has remained essentially unchanged for several years. The patient is not suffering from any concomitant disease. Although he has had one or more attacks of acute myocardial infarction, his economic status and occupation are such that, if relieved of some or all of his cardiac pain, he will not feel compelled to engage in arduous physical work. Physical examination discloses no significant abnormalities. The blood pressure is normal or slightly elevated. The basal metabolic rate is above −10 per cent. Examinations of the blood, urine and stools reveal normal findings. Although a good therapeutic result is not invariable, our experience demonstrates that well over half of such patients will experience worthwhile improvement.

Pre- and Post-Treatment Management

Radioactive iodine therapy for euthyroid cardiac patients, as previously stated, is to be regarded as an adjunct; the patient's cardiac condition must continue to be treated with the same painstaking care previously exercised. Before administering I^{131}, we have placed the patients on a low iodine diet and have assured ourselves that stable iodine has not been received by the patient. The most common sources of iodine are in cough or other medicines, gall-bladder dye, antiluetic drugs or iodized salt. We have explained the present investigative nature of this form of therapy to our patients and have administered tracer doses of 100 or 150 microcuries. A dose of approximately 40 millicuries in our experience is usually effective in producing myxedema. To obviate the discomfort of possible thyroiditis, we recently have increased the total dose slightly and administered it in three divided doses at ten- to fourteen-day intervals. Twenty-four hourly collections of urine for three days following the tracer dose and again following each therapeutic dose have been measured for I^{131} content. In some patients, the amount of I^{131} uptake by the thyroid has been measured directly by the method devised by one of us.[12]

If the patient has a thyroid nodule, the possibility exists that I^{131} will destroy the normal thyroid tissue, following which the adenoma may take on function. In at least one instance, however, the single initial therapeutic dose affected the nodule as well as the normal tissue with resultant hypothyroidism. In other patients, additional doses may be required to effect destruction of the adenoma.[13]

With the appearance of hypothyroidism, it has been our practice to permit frank myxedema to develop in order to learn the effects of I^{131} uncomplicated by other medication. It is possi-

ble that patients may be safeguarded from some of the unpleasant symptoms of myxedema by administering small doses of thyroid before they reach markedly lowered levels of metabolic rates below −30 per cent. In a patient recently treated, but not included in this series, we have administered 6 mg. of thyroid daily after the basal metabolic rate had declined from −5 per cent to −20 per cent, at which latter level the patient was conspicuously relieved of attacks of angina pectoris but showed no discomfort from hypothyroidism.

Patients with myxedema are remarkably responsive to small doses of thyroid. The optimum metabolic rate level for each patient varies somewhat but is usually between −15 and −25 per cent. Fifteen milligrams of thyroid is usually sufficient to maintain this level, but in some patients only 6 mg. is necessary. Depending on the metabolic rate level and the severity of the symptoms of myxedema, if present, it has been our practice to initiate thyroid medication in doses of either 6 or 12 mg. daily (1/10 to 2/10 grain). In some patients, higher doses of thyroid are necessary, as in Case 14 who was maintained by daily thyroid doses of 90 mg. at a level of −15 per cent, compared to a pretreatment level of +20 per cent. In general, it has been our practice to begin with small doses and to raise the amount administered in accordance with the patient's symptomatology, basal metabolic rate measurements, and at times determination of the serum cholesterol concentration. All patients should be seen at least once a month, since it is entirely unnecessary for a patient to suffer from the distressing symptoms of myxedema.

Most patients feel so much better that they must be warned against overexertion. This procedure does not alter the underlying pathological process, and so it is important that they should not overtax themselves. Three of our patients, because of economic necessity, are working eight to twelve hours a day. While this is not advisable under ideal circumstances, 2 of the patients are highly intelligent and although performing manual labor, one as a foreman of bricklayers, and the other as a laboratory assistant, they are careful to avoid intense effort.

The social-economic problems in our patients have been many. While some patients must be warned not to overdo, others have their previous suffering so vividly before them that they must be encouraged to develop self confidence and undertake moderate exercise. Fear of recurrence of angina pectoris or congestive failure in some patients presents a serious psychologic problem. Some patients, supported by other members of the family for years, are faced with the necessity of becoming self reliant and independent on being relieved of their angina pectoris or congestive failure.

Problems Requiring Further Study

The final appraisal of this new therapeutic procedure awaits the results attained in numerous patients with various types of cardiovascular disease. Whether the duration of life is actually prolonged by this treatment can only be ascertained by studying the subsequent history of these patients over their entire clinical course. From our previous experience with total thyroidectomy, it would appear that in any case, duration of life is not shortened, and that undoubtedly many months of a worthwhile and comfortable existence already have been added to these invalided cardiac patients, many of whom have suffered greatly from recurrent attacks of angina pectoris, paroxysmal dyspnea, acute pulmonary edema, and the distressing symptoms of congestive failure.

Our previous experience with total thyroidectomy, as well as the results in Case 8, indicate that concomitant diabetes mellitus is ameliorated as judged by the lessened insulin requirement.

The hypothyroid state involves complex relationships between the thyroid, pituitary, adrenals, gonads and other endocrines. In accordance with our previous experience with total thyroidectomy, we have observed in the hypothyroid state that some of our patients became less irritable and more stable emotionally, a fact which suggests that induction of myxedema may be helpful in the care of unmanageable, disturbed psychotic patients who require forcible feeding and constant restraint.

The marked variation displayed by different patients in the symptomatology of myxedema suggests that the effects of the hypothyroid

state on the other endocrine glands may be responsible for some of these symptoms. If this proves to be the case, and if substitution therapy for the hypofunction of other endocrine organs can be given without raising the metabolic rate, some patients might be maintained in comfort at a lower and more beneficial metabolic rate. This problem is receiving further study by us and it is hoped that other investigators may also bend their efforts in this direction.

Summary and Conclusions

1. The therapeutic results of hypothyroidism induced by radioactive iodine in 18 euthyroid patients with intractable advanced angina pectoris or congestive heart failure are reported. The duration of post-treatment observation was seven to twenty-four months and averaged thirteen months.

2. Persistent hypothyroidism can be regularly induced by one or more appropriate doses of radioactive iodine (I^{131}).

3. No radiation sickness and no toxic effects on the blood or kidneys have been observed. Mild or moderate transitory thyroiditis occurred in ten patients, was severe in only one and was absent in seven. Temporary mild hyperthyroidism occurred in 2 patients.

4. Each patient received orally a total of 25.5 to 150 millicuries in single or divided doses, of which a total of 7.3 to 39 millicuries was retained within the body during the following seventy-two hours. The largest single dose was 56 millicuries.

5. The average total dose was 54.4 millicuries; the average three day retention, 17.9 millicuries.

6. Only patients were treated who were seriously incapacitated despite all standard forms of therapy and marked restriction of activities for many months or years.

7. Angina pectoris has been strikingly lessened or abolished in 8 of the 13 patients with intractable cardiac pain. Several patients have been rehabilitated and are gainfully employed. Concomitant congestive failure present in several of these patients was likewise improved. In the other 5 of the 13 patients, angina pectoris was greatly relieved when the patients were myxedematous but recurred when thyroid was administered to ameliorate the discomfort of myxedema.

8. Three of 5 patients incapacitated primarily because of congestive heart failure have shown worthwhile improvement; in 2 of these the improvement has been striking.

9. Tentative criteria for the selection of patients are presented, and the pre- and post-treatment management of the clinical course is described.

10. In the clinical management of these patients, we have attempted to maintain the lowest metabolic rate consistent with the comfort of the patient and have administered small doses of thyroid after the induction of myxedema.

11. This group represents the intractable cardiac cripples who are ordinarily considered for surgery. Hypothyroidism induced by radioactive iodine promises to accomplish worthwhile improvement through medical means without the inevitable risk and complications of surgical intervention.

12. This procedure is therefore proposed as a means of treating angina pectoris and congestive failure refractory to the standard medical measures and is submitted for further investigation by other workers in this field.

13. Final evaluation of this therapy must await prolonged study. At present it can be said that many months of worthwhile existence already have been added to the lives of these disabled cardiac patients who were refractory to all standard forms of medical therapy.

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Relation of Basal Metabolic Rate to Vasodilatation and Vasoconstriction of the Extremities of Normal Subjects as Measured by Skin Temperatures

By GRACE M. ROTH, PH.D., AND CHARLES SHEARD, PH.D.

Various indirect methods of measuring blood flow in the peripheral blood vessels of man are available. Irrespective of the method used for measuring blood flow, certain fundamental factors concerned with the status of the subject or patient influence the measurement of blood flow. These factors are environmental temperature, position of the extremities and food. The present investigation indicates that a consideration of the basal metabolic rate or basal heat production is another important factor.

THE MEASUREMENT of blood flow in the peripheral blood vessels of the extremities of man is necessarily indirect. The plethysmograph, which measures the changes in volume of the extremity, the calorimeter, which measures the amount of heat given off from the extremity to a known amount of water, and thermocouples and radiometers, which measure changes in skin temperatures of the extremities, have become available for these measurements. We believe that certain fundamental factors influence the blood flow in the peripheral blood vessels of the extremities of man and that further consideration of these factors is necessary when studies of blood flow are made.

We[3,5] have shown previously by use of thermocouples that the control of environmental temperature and the intake of food are important factors in the control of the heat-regulating mechanism and particularly in the production of vasodilatation. Also, the position of the extremity may play a role. We also believe that the basal heat production must play an important role in the consideration of vasoconstriction and vasodilatation.

In 1933, Maddock and Coller[2] demonstrated a simple linear relationship in the same individual between the skin temperatures of the great toe and the basal heat production per unit of surface area. In 1940, Sheard and Williams,[6] studying a small group of normal individuals under specified standard environmental conditions, found a similar linear relationship but with some indication of a twofold division or dual character. Since, in both instances, the number of subjects observed was not large, we have extended this investigation to include a much greater number of subjects. Furthermore, the question has arisen as to whether there is any relation between the basal metabolic rate and the amount of cooling of the extremities during vasoconstriction or the amount of warming of the extremities during vasodilatation.

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PROCEDURE

Basal metabolic rates and skin temperatures of the fingers and toes were determined on 189 normal subjects. The group consisted of 159 men and 26 women between the ages of 20 and 50 years. In addition, studies were made on 2 boys of 12 years of age, a man of 51 years and another of 70 years. Before the tests the subjects fasted for fifteen hours and during the tests they wore lightweight, short pajamas and lay supine on a comfortable bed in a constant temperature room kept at 25.5 C. (78 F.) with a relative humidity of 40 per cent.

The basal metabolic rates were determined by a modification of the Tissot gasometric method, and the expired air was analyzed in a Haldane gas analyzer. The tests were made just before or during the control period when the measurements of the skin temperatures were being made.

In 27 of these normal subjects, subsequent to the control studies made in a constant environmental temperature of 25.5 C. (78 F.), vasoconstriction was determined by measurement of the cutaneous temperatures of the extremities when the subject was moved to a cooler environment of 20 to 21 C. (68.0 to 69.8 F.) and a relative humidity of 40 per cent. After remaining in this environment for an hour, the subject was moved to a warmer environment of 30 to 32 C. (86 to 89.6 F.) and remained there for an-

other hour, and the degree of vasodilatation was determined from the changes in the cutaneous temperature of the extremities. In 13 additional subjects vasodilatation was determined by moving the subject from the constant temperature room of 25.5 C. (78 F.) to the warmer environment of 30 to 32 C. (86 to 89.6 F.) for an hour. Since it has been shown by several investigators that vasodilatation is produced by the ingestion of a substantial meal, we also measured skin temperatures of the extremities and metabolic rates before and after the ingestion of food in 10 of these normal subjects.

square meter of surface area per hour for 189 normal subjects whose ages ranged from 12 to 70 years is shown in figure 1. There is a definite indication of a dual linear relationship between the metabolic rates and the skin temperatures, since the plotted points fall into two divisions indicated by the heavy lines with a minimal density of points in the region of the broken line. Since the relationship between the values of the abscissas and ordinates is linear,

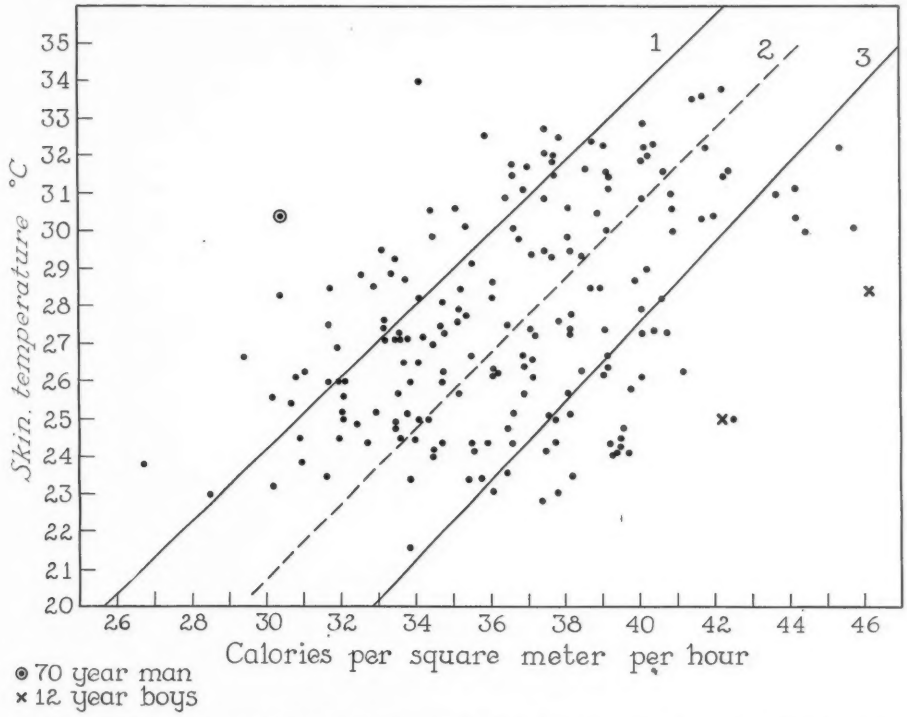

FIG. 1.—The relationship between the average skin temperature of the toes and the calories per square meter of surface area per hour for 189 normal subjects. Equations for lines 1, 2 and 3 are given in the text.

The temperatures of the plantar surface of the first and third toes of both feet and the volar side of the distal phalanges of the first and third fingers of both hands were determined by means of copper-constantin thermocouples. The observations were made at intervals of ten minutes for three to four hours. The presence or absence of sweating of the extremities was noted in all cases.

RESULTS

The relationship between the average skin temperatures of the toes and the calories per

it may be expressed as $x = ay + b$. The equations for the three lines in figure 1 are: (1) $x_1 = 1.18\ y_1 + 1$; (2) $x_2 = 1.18\ y_2 + 4$; and (3) $x_3 = 1.18\ y_3 + 6$. The lowest basal rate of any subject was 26.8 calories per square meter per hour in a man aged 21 years, and the highest rate of 45.8 calories per square meter per hour was found in a man aged 25 years. The rate for the 2 boys was 46.2 and 42.2 calories per square meter per hour respectively,

and that for the 70 year old man was 30.4 calories per square meter per hour. The lowest skin temperature of the toes was 21.6 C. (70.7 F.) in the man aged 21 years, who also had cold, clammy feet, and the highest temperature was 34 C. (93.2 F.) in a man of 39 years with hot, dry feet.

The mean basal production of heat and the mean skin temperature of the toes of the subjects are grouped in table 1 according to the ages of the individuals as well as according to sex. There was a significant difference in the mean calories per square meter per hour between the ages of 20 to 29 years and 30 to 39 years and again between the ages of 30 to 39 years and 40 to 49 years. The slight decrease in the calories per square meter per hour in the 30 to 39 year group when compared with the other two age groups was not accompanied in our subjects by a decrease in the mean skin temperature of the toes. On the contrary there was a small increase in the mean skin temperature of the toes over the 20 to 29 year group. The smaller mean number of calories per square meter per hour of women in contrast to men found its counterpart in a slight but significant lower mean skin temperature of the toes.

TABLE 1.—*The Mean Basal Heat Production and the Mean Skin Temperature of the Toes of Subjects Grouped According to Age and Sex*

Age group, yr.	Cases	Mean B.M.R.			Mean skin temperatures	
		Per cent	Calories per square meter per hour	Standard deviation	Degrees C.	Standard deviation
20–29	133	−9.9	36.9 ± 0.3*	3.7	27.1 ± 0.3	2.7
30–39	44	−8.3	35.3 ± 0.4	2.8	28.4 ± 0.4	2.8
40–49	8	−1.0	37.9 ± 1.4	3.8	30.7 ± 1.1	3.2
All Groups	185	−9.1	36.6 ± 0.3	3.7	27.6 ± 0.2	2.8
Men						
20–39	151	−9.8	37.0 ± 0.3†	3.4	27.6 ± 0.2‡	2.8
Women						
20–39	26	−7.0	33.5 ± 0.6	3.1	26.1 ± 0.4	2.0

* $t < 0.001$; † $t < 0.001$; ‡ $t = 0.001$.

The curves of figure 2 show the increase of the skin temperatures of the toes as well as of the metabolic rates in 2 individuals after the ingestion of a substantial meal; one of these individuals had a high (42.4 calories per square meter per hour) and the other a low (33.8 calories per square meter per hour) initial basal metabolic rate. A greater period of time was required to obtain a maximal vasodilatation in the toes of the subject with the lower basal metabolic rate. The mean for the group of 10 subjects before the meal was 36.9 calories per square meter per hour and 27.3 C. (81.2 F.) for the temperatures of the toes, whereas the mean after the meal was 44.7 calories per square meter per hour and 32.3 C. (90.2 F.) for the skin temperatures of the toes. Individually the basal metabolic rates of these subjects ranged from 30.6 to 42.4 calories per square meter per hour prior to the ingestion of the meal and from 33.8 to 50.1 calories per square meter per hour after the meal, and the skin temperatures of the toes ranged from 22.5 to 31.6 C. (72.5 to 88.8 F.) before taking food to 30.2 to 34.3. C. (86.4 to 93.8 F.) after the meal.

The data in table 2, covering 40 normal subjects grouped according to basal heat production, show the average periods of time necessary to produce a state of vasodilatation indicated by a rise of the skin temperature of the toes to 33 C. (91.4 F.) in the warm room. As the basal heat production increases, the period of time necessary to produce vasodilatation of the toes decreases. The data of table 3, obtained on 27 normal subjects grouped according to the basal rate of heat production, show the periods of time required to produce vasoconstriction, as indicated by a skin temperature of the toes of 20 C. (68 F.), in an environmental temperature of 20 C. (68 F.).

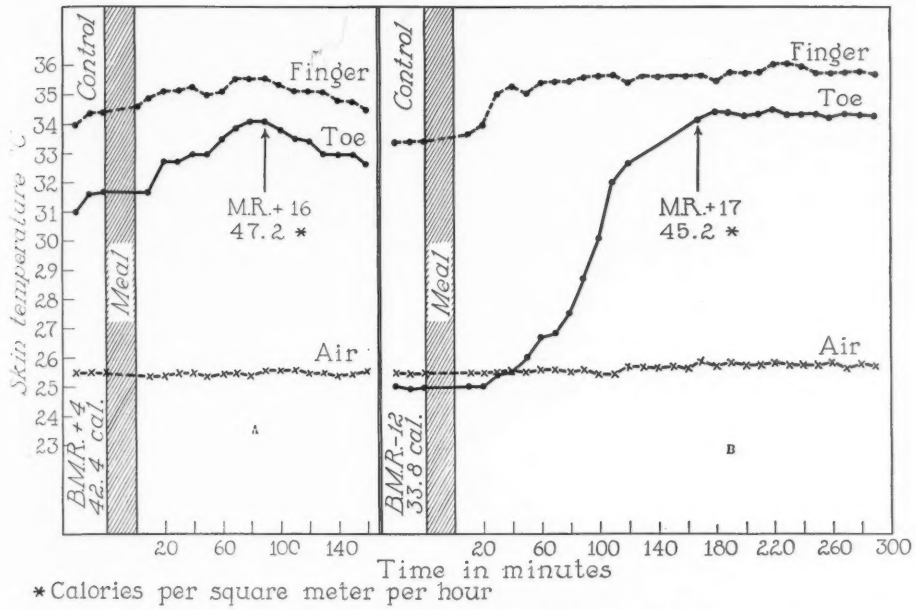

FIG. 2.—The increase of the skin temperatures of the toes as well as the metabolic rate after the ingestion of a substantial meal in two normal individuals. *A*, The subject with high basal heat production. *B*, A subject with a low basal heat production. The curves show a delay in the rise in the skin temperatures of the toes in the subject with the lower basal heat production.

TABLE 2.—*Time Necessary to Produce Vasodilatation in a Warm Room as Evidenced by an Increase of the Skin Temperature of the Toes to 33 C. (91.4 F.) of Forty Normal Subjects Grouped According to the Basal Metabolic Rate*

Subjects	B. M. R., calories per square meter per hour	Time, min.	Skin temperature of toes, degrees C.
4	31–34.9	180	33
23	35–39.9	93	33
10	40–44.9	60	33
3	45–49.9	25	33

TABLE 3.—*Time Necessary to Produce Vasoconstriction in a Cool Room at 20 C. (68 F.) as Evidenced by a Decrease of the Skin Temperature of the Toes to 20 C. (68 F.) of Twenty-seven Normal Subjects Grouped According to the Basal Metabolic Rate*

Subjects	B. M. R., calories per square meter per hour	Time, min.	Skin temperature of toes, degrees C.
4	30–34.9	38	20
17	35–39.9	73	20
6	40–44.9	108	20

Under these conditions, the greater the initial production of heat the longer it takes to produce vasoconstriction in the toes. In 8 other subjects, with basal heat productions ranging from 40.8 to 50.1 calories per square meter per hour subjected to the same cool environmental temperature of 20 C. (68 F.), it was found that, after ninety to one hundred and twenty minutes of exposure, the decrease of the skin temperature of the toes ranged from 3.9 to 9.4 C. (7 to 16.9 F.) above the environmental temperature. This decrease indicated that some degree of vasoconstriction had occurred, but not as much as in the other subjects with lower basal heat production.

The curves of figure 3 show the effects of moist extremities on the skin temperatures of the toes of 2 normal individuals, one with a rather low (−14 per cent) basal metabolic rate and the other with a higher rate (−3 per cent). The data in both instances show that, with damp feet, the temperatures of the toe remained constant but 1 to 1.5 C. (1.8 to 2.7 F.) below the room temperature.

When the subjects were placed in an environmental temperature of 28 C. (82.4 F.) with relative humidity of 40 per cent, the extremities of the individual with higher basal metabolism (fig. 3, *A*) became normally dry, vasodilatation of the extremities occurred as is evidenced by the increase in temperature of the toe and, in the course of an hour, a condition of maximal vasodilatation was exhibited. In the individual with the lower metabolic rate (fig. 3, *B*), the feet were still damp in an atmosphere of 28 C. (82.4 F.) and vasoconstriction of the extremities, particularly in the feet, was present. However, a change of 1.5 C. of the environmental temperature (from 28 to 29.5 C. or 82.4 to 85.1 F.), produced normal dryness of the extremities, followed by normal vasodilatation as is evidenced by the skin temperatures of the fingers and of the toes.

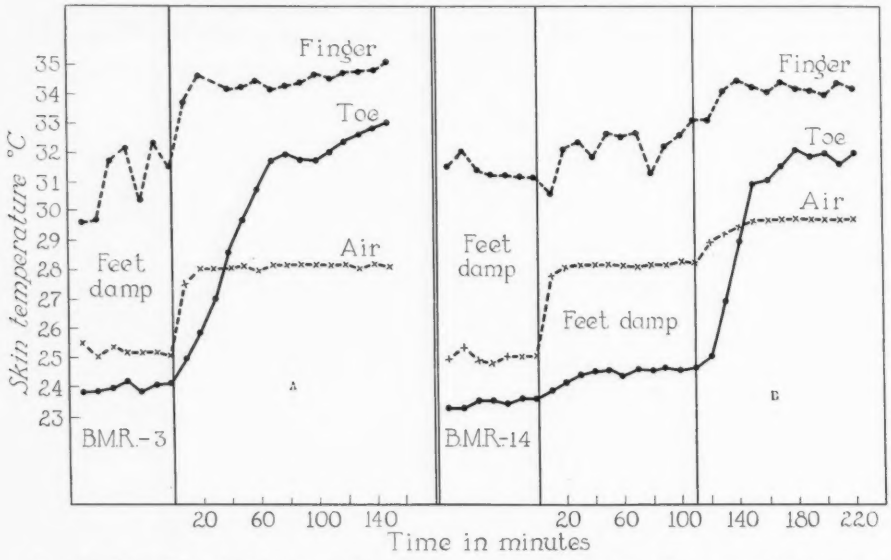

FIG. 3.—The effect of moisture on the skin temperatures of the toes of two normal subjects. *A*, Subject had a low basal metabolic rate. *B*, A higher basal metabolic rate. The curves show a delay in vasodilatation of the feet in the subject with the more moist extremities and the lower metabolic rate.

COMMENT

Production of heat in the body must equal loss of heat from the body if the internal temperature is to be maintained at a constant value. The metabolic rate is a measure of the production of heat. The dissipation of heat is carried on by the processes of radiation, evaporation, conduction and convection. If the losses due to convection, conduction and evaporation are controlled and kept constant under specified environmental conditions, then the additional losses of heat may be measured by radiometers or thermocouples, since both instruments may be used to measure the temperatures of various areas of the body. As has been pointed out in other contributions,[5] the skin temperatures of the toes are the most sensitive or delicate indicators of the vasomotor regulation of the dissipation of heat under any environmental conditions in which vasomotor regulation is the chief and, ideally, the only source of regulation. If, however, areas of the body, and particularly the lower extremities, are moist, then regulation of loss of heat is accomplished in part by evaporative losses. Hence, in individuals with the same basal metabolic rates it would be expected that the skin temperatures of the toes would be lower among those with moist extremities. The data plotted in the diagram (fig. 1) give

the experimentally obtained relationship between the skin temperatures of the toes and the calories per square meter per hour, and show a definite tendency to be grouped into two divisions. This dual grouping is dependent primarily on the degree of dryness or dampness of the surface of the body.

When metabolic rates are changed by the ingestion of food, and the subjects are kept under constant standard environmental conditions, the rates of increase of the temperatures of the toes are fairly closely proportional to the basal heat production. The foregoing statement also holds when individuals in the basal state are moved from a standard environment of 25.5 C. (78 F.) to a warm room (31 C., or 87.8 F.).

Stewart and Evans[7] also demonstrated in normal subjects that under basal conditions at an environmental temperature of 25 C. (77 F.), peripheral blood flow is usually less with a lower basal metabolic rate and greater with a higher basal metabolic rate.

Kirklin, Plummer and Sheard[1] reported measurements of skin temperature in cases of exophthalmic goiter before and after administration of strong solution of iodine (Lugol's solution) and before and after partial thyroidectomy. They found that with a reduction of basal metabolic rate following either the administration of Lugol's solution or partial thyroidectomy there is a reduction in the skin temperature of the toes.

Also, Roth, Williams and Sheard[4] found that, with production of thiamine deficiency, measurements of skin temperature at various times during the period of restriction showed a more or less close correlation with the basal metabolic rates, rather than with the severity of the clinical symptoms.

Summary

The experimental data given in this paper, as well as the evidence furnished by other approaches to the problem, show the importance of a consideration of basal heat production in studies concerning vasodilatation or vasoconstriction as measured by skin temperatures of the extremities in normal subjects or patients with pathologic conditions.

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The Effect of Nicotinic Acid on the Cerebral Circulation, with Observations on Extracerebral Contamination of Cerebral Venous Blood in the Nitrous Oxide Procedure for Cerebral Blood Flow

By Peritz Scheinberg, M.D.

Measurement of cerebral blood flow by the nitrous oxide method before and during intravenous administration of nicotinic acid indicates that cerebral vessels do not respond to this drug. Evidence that contamination of cerebral by extracerebral blood occurs in about 20 per cent of subjects is adduced from the effects of nicotinic acid on the measured cerebral blood flows; studies making use of the intravascular catheter technic to sample internal jugular blood tend to confirm this hypothesis.

THE NITROUS oxide method for measuring cerebral blood flow, as devised by Kety and Schmidt,[1] is based on the assumption that the blood collected from a needle placed in the internal jugular bulb is not significantly contaminated by blood from extracerebral sources. This problem was investigated by Shenkin, Harmel and Kety,[2] who calculated the percentage contamination of internal jugular by extracerebral blood by injecting dye into the external carotid artery and drawing blood samples from the internal jugular bulb and external jugular vein. They concluded that in the 8 subjects studied, an average of only 3 per cent of the blood in the internal jugular bulb is derived from extracerebral sources. These data are useful in studying normal subjects at ordinary room temperatures; they do not help in determining whether contamination has occurred in any given subject. Furthermore, it appeared possible that the frequency and degree of contamination might be different when the vessels of the extracerebral circulation were widely dilated, as following local heating or the administration of various drugs. Since nicotinic acid produces an intense flushing of the face, scalp, and neck and is thought to produce an increase in blood flow in these areas, this drug was employed with the following objectives in mind: (1) To determine the effect of nicotinic acid on the cerebral circulation; (2) to determine the frequency and extent of contamination of internal jugular by extracerebral blood; and (3) to devise a simple test to determine whether contamination had occurred in any given subject.

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Method

The subjects were chosen at random from the hospital wards and included patients with various disease states, as well as 2 normal subjects. While several of the patients showed evidence of chronic cerebral vascular disease, none were studied immediately after an acute cerebral vascular accident. All the subjects were studied under fasting conditions. The nitrous oxide procedure for measuring the cerebral blood flow has been described in detail by Kety and Schmidt,[1] and the modification in use in this laboratory of drawing continuous ten minute blood samples simultaneously from the femoral artery and the internal jugular bulb for the determination of the mean arterio-venous nitrous oxide difference has been reported previously,[3] together with data on values for normal young subjects. The gas mixture used in the determination consisted of 15 per cent N_2O, 64 per cent N_2 and 21 per cent O_2. Arterial pressures were measured by the auscultatory method, with the arm held at heart level, every two minutes during the blood flow determination. Mean pressures were calculated from these readings by adding one-third the pulse pressure to the diastolic pressure. Blood oxygen contents were determined by the spectrophotometric method of Hickam and Frayser.[4] Glucose was determined by Nelson's photometric adaptation of the Somogyi method.[5] Cerebral oxygen utilization, cerebral glucose utilization, and cerebrovascular resistance were calculated as previously described. [1, 3]

The nicotinic acid was administered intravenously

in a normal saline infusion; doses of 300 to 800 mg. in 200 to 300 ml. of saline, over a twenty- to twenty-five minute period were used. In all instances, a very pronounced flush was produced over the blush area, with lesser degrees of flushing over other parts of the body. The control blood flow determination was always done prior to the administration of nicotinic acid.

Results

Effect of Nicotinic Acid on the Cerebral Circulation. The data are presented in table 1. Intravenous nicotinic acid in large, flushing doses produced no significant change in any of the cerebral metabolic functions. The relatively large standard errors are the result of the heterogeneity of the population studied. Taken in this way, these nicotinic acid studies are of no great positive value. Examination of figure 1, however, reveals a finding of interest. This chart plots, for comparison, the individual determinations of cerebral blood flow and A-V O_2 difference expressed as percentage change from the control values resulting from the administration of nicotinic acid or procaine block of the stellate ganglion. The latter results are taken from a previous study.[6] The spread of the changes occurring from these two procedures (neither of which revealed statistically significant change when considered as a group) are about the same except for the determinations enclosed in the blocks. These subjects showed changes following the administration of nicotinic acid which were strikingly different from the whole group; two of the subjects showed large changes in cerebral blood flow, whereas four had significant changes in A-V O_2 difference. The large decreases in A-V O_2 difference in these 4 subjects (out of a group of 20) suggest that in approximately one out of 5 persons the cerebral vessels are dilated by the nicotinic acid, or that the internal jugular blood is contaminated by extracerebral blood. The results to be reported strongly support the thesis of extracerebral contamination.

It should be pointed out that within wide limits the oxygen consumption of areas drained by the internal and external jugular veins is not changed by increasing the blood flow. As the calculated blood flow increases, the arteriovenous oxygen difference falls, and the product of the two remains the same. It is important to emphasize that the finding of a constant cerebral oxygen consumption before and after the administration of nicotinic acid does not bear on the question of contamination. It will be noted that blood flow studies before and during nicotinic acid were obtained on only 3 of the 4 subjects in whom the arteriovenous oxygen difference decreased during nicotinic acid. In 2 of these 3, the calculated cerebral blood flow during nicotinic acid increased proportionately and oxygen consumption was not changed. In the one instance in which the calculated blood flow did not increase, the fall in oxygen consumption was 0.8 ml. O_2 per minute per 100 Gm. brain, a change which is probably in the range of variation due to technical inaccuracies. As mentioned before, when the patients are considered as a group, there was no significant change in cerebral oxygen consumption.

The Nitrous Oxide and Oxygen Content of Blood Draining from the Face and Neck. These data are summarized in table 2. The blood flow procedure and calculations were performed in the same way as the cerebral blood flow, except that venous blood was drawn from the external jugular vein or from the internal jugular vein about 5 cm. inferior to the jugular bulb. This gives a value for blood flow which does not represent facial blood flow, as the solubility coefficient for nitrous oxide in the tissues of the face and neck is unknown, and it is doubtful if the facial and neck tissues are homogeneous enough to make the nitrous oxide method applicable. It does indicate the direction of error which results if blood from these tissues are mixed with blood draining from the brain. The nitrous oxide and oxygen contents of the external jugular blood were studied in eight observations on 7 subjects. The calculated average blood flow was 29 ml. per minute per 100 Gm. tissue, less than half of the expected average cerebral blood flow; the average A-V O_2 difference was 2.96 volumes per cent, less than half of the expected average cerebral A-V O_2 difference. Thus, contamination from facial and neck blood ordinarily gives a falsely low value for cerebral blood flow and cerebral O_2 consumption.

TABLE 1.—*The Effects of Intravenous Nicotinic Acid on Cerebral Metabolic Functions*

Pt.	Age	Diagnosis	Cerebral Blood Flow (ml./min./100 Gm. brain)		Arterial-Cerebral Venous O_2 Difference (vol. %)		Arterial-Cerebral Venous Glucose Difference (mg. %)		Cerebral O_2 Consumption (ml. O_2 min./100 Gm. brain)	
			Before N.A.	During N.A.	Before N.A.	During N.A.	Before N.A.	During N.A.	Before N.A.	During N.A.
S. C.	50	Pernicious anemia	36		6.10	4.37	12	12	2.19	
H. S.	55	HVD; Diabetes	48	49	5.92	4.16	11	8	2.88	2.08
T. M. S.	48	Cerebral vasc. dis.	48	43	8.75	8.80	14	10	4.20	3.80
C. P.	49	Cerebral vasc. dis.	39	38	8.65	8.60	18	18	3.37	3.27
M. S.	23	RHD and Congestive heart failure	49	82	5.15	3.05	11	8	2.53	2.51
E. G.	58	Myxedema	40	43	6.47	6.35	18	15	2.59	2.73
W. P.	60	Pernicious anemia	25	45	2.56	2.53	9	7	0.65	1.14
W. W.	28	RHD; Congestive heart failure	41	35	9.28	9.06	15	15	3.80	3.17
T. R.	42	HVD	58	57	6.48	6.75	12	13	3.76	3.84
C. L.	23	Hysteria	76	95	4.52	4.05	12	7	3.43	3.84
H. F.	45	HVD	48	46	6.55	7.35	11	12	3.14	3.38
J. W.	36	HVD	65	69	4.54	4.15			2.95	2.87
N. B.	26	HVD	84	74	5.84	5.84	8	11	4.90	4.40
A. S.	29	Normal	61	62	6.78	7.04	11	12	4.14	4.36
M. S.	19	Hysteria	64	58	6.03	5.95	6	5	3.76	3.45
J. B.	33	Normal	78	87	5.11	5.42	5	8	3.99	4.71
M. M.	54	Myxedema	54	67	7.15	5.16	12	11	3.86	3.79
G. H.	39	HVD	54	52	8.21	8.43	15	11	4.43	4.40
M. L.	32	HVD	50	40	8.11	8.40	11	11	4.10	3.40
H. S.	50	HVD	48	45	6.40	5.60	8	6	3.06	2.50
Mean			54	57	6.40	6.04	11.3	10.5	3.39	3.34
St. Dev.†			14.6	17.5	1.6	2.7	3.53	3.33	0.92	0.89
St. Error‡			3.3	4.1	0.35	0.59	0.79	0.74	0.21	0.20

Pt.*	Cerebral Glucose Consumption (mg. glucose/min./100 Gm. brain)		Mean Arterial Pressure (mm. Hg)		Cerebral Vascular Resistance (units)	
	Before N.A.	During N.A.	Before N.A.	During N.A.	Before N.A.	During N.A.
S. C.	4.32		91		2.53	
H. S.	5.28	3.92	107	95	2.23	1.93
T. M. S.	6.72	4.30	125	121	2.60	2.81
C. P.	6.82	6.84	155	129	3.97	3.40
M. S.	5.14	6.14	87	77	1.77	0.77
E. G.	7.20	6.46	137	125	3.42	2.91
W. P.	2.25	3.15	91	86	3.64	1.91
W. W.	6.15	5.25	100	97	2.44	2.77

* For age and diagnosis, see top half of table.

† Standard deviation = $S = \sqrt{\frac{Sx^2 - \frac{(Sx)^2}{n}}{n-1}}$

‡ Standard error = $S/\sqrt{n}$

HVD = Hypertensive vascular disease

RHD = Rheumatic heart disease

N. A. = Nicotinic Acid

The p values, calculated from the changes resulting in individual cases following nicotinic acid administration, range from 0.06 to 0.35, indicating that the changes are not statistically significant.

Formula: $t = \frac{\text{Mean difference}}{\text{Std. error of mean diff.}}$

TABLE 1.—*Continued*

Pt.	Cerebral Glucose Consumption (mg. glucose/min./100 Gm. brain)		Mean Arterial Pressure (mm. Hg)		Cerebral Vascular Resistance (units)	
	Before N.A.	During N.A.	Before N.A.	During N.A.	Before N.A.	During N.A.
T. R.	6.96	7.40	181	158	3.07	2.77
C. L.	8.36	6.65	91	87	1.20	0.92
H. F.	5.28	5.52	158	157	3.29	3.41
J. W.			133	129	2.05	1.87
N. B.	6.72	8.10	123	124	1.47	1.68
A. S.	6.40	7.75	93	93	1.50	1.50
M. S.	3.96	2.90	74	71	1.12	1.22
J. B.	4.20	6.80	68	69	0.87	0.80
M. M.	6.30	7.20	119	122	2.20	1.80
G. H.	8.10	6.20	113	115	2.10	2.20
M. L.	5.40	4.40	126	121	2.50	3.10
H. S.	3.80	2.90	115	110	2.40	2.45
Mean	5.83	5.66	114	109	2.32	2.12
St. Dev.	1.58	1.69	29	26	0.88	0.82
St. Error	0.37	0.40	6.5	5.8	0.2	0.19

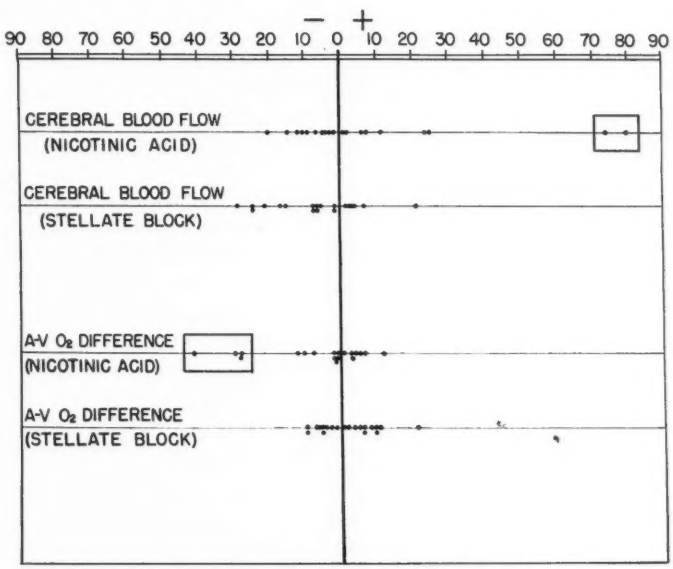

FIG. 1.—Individual determinations of cerebral blood flow and A-V O_2 difference, expressed as percentage change from the control values resulting from the administration of nicotinic acid or procaine block of the stellate ganglion.

In 5 subjects given nicotinic acid, the flow calculated from blood in the external jugular vein increased from an average of 29 to 91 ml. per minute per 100 Gm. tissue. (It must be remembered that this does not represent true blood flow, but rather an increase in the nitrous oxide content of the venous blood.) Of these, only two subjects (J. W. and L. J., table 2) showed an increase to levels that would have caused a significant increase in the cerebral blood flow above normal had this blood been contaminating cerebral venous

blood. The others would have caused only a small increase in the original cerebral blood flow, and might not be recognized because of the errors inherent in the method. The average A-V O_2 difference in these 5 subjects fell from 3.0 to 0.9 volumes per cent, and in every instance the change was striking and would have produced a falsely low A-V O_2 difference if this blood had been contaminating cerebral venous blood. The mean oxygen consumption of the tissues drained by the external jugular vein was not altered significantly by the nicotinic acid. In Subject L. J., blood was obtained from the internal jugular bulb simultaneously with that taken from the external jugular vein; there was no change in either cerebral blood flow or A-V O_2 difference with nicotinic acid, indicating that no contamination was present.

In 3 subjects, a catheter was inserted into the internal jugular vein under fluoroscopic observation to a point 5 cm. inferior to a needle which had been placed in the internal jugular bulb of the same side. Simultaneous samples were taken from the needle and catheter. The position of the catheter was intended to allow it to receive blood from the internal jugular vein at a point inferior to the entrance of the common facial vein into the internal jugular. Blood from the needle should have represented that from the brain, blood from the catheter a mixture of blood from the brain and face.

TABLE 2.—*Comparative Blood Flows and Arteriovenous Oxygen Differences when Venous Blood is Obtained from the Internal Jugular Bulb, Internal Jugular Vein, and External Jugular Vein*

Pt.	Age	Type of Procedure	Blood Flow (ml./min./100 Gm. tissue)						Arteriovenous O_2 Difference (volumes %)					
			Before N.A.			During N.A.			Before N.A.			During N.A.		
			I.J.B.	Cath.	E.J.V.	I.J.B.	Cath.	E.J.V.	I.J.B.	Cath.	E.J.V.	I.J.B.	Cath.	E.J.V.
L. B.	38	External jugular blood flow			20						2.60			
J. S.	30	External jugular blood flow			27						2.78			
					35						2.33			
J. M.	44	External jugular blood flows, before and during N.A.			18			57			2.43			0.90
J. W.	34	Same as above			46			128			0.97			0.48
N. S.	44	Same as above			37			47			5.24			1.25
Z. B.	40	Same as above			23			53			4.82			1.44
L. J.	20	Simultaneous int. and ext. jug. blood flows, before and during N.A.	67		29	57		172	5.74		2.50	5.80		0.33
R. C.	25	Catheter in int. jug. vein. Needle in int. jug. bulb. Simultaneous blood flows before and during N. A.	42	30		38	39		7.65	7.20		7.87	4.46	
R. D.	33	Same as above (oxygens only)							7.49	5.96		7.46	1.84	
H. S.	50	Same as above	48	18		45	26		6.40	4.03		5.60	2.96	
Mean			52	24	29	47	33	91	6.82	5.73	2.96	6.68	3.09	0.88

I. J. B. = Internal Jugular Bulb.
Cath. = Catheter.
E.J.V. = External Jugular Vein.
N.A. = Nicotinic Acid.

Nicotinic acid increased the blood flow and decreased the A-V O_2 difference when calculated from samples collected by the catheter. In 2 patients, the oxygen content of the blood from the needle was unchanged; in one it rose. In this instance, the assumed contamination from extracerebral blood did not change the calculated flow.

The observations indicate that contamination from extracerebral sources consistently decreases the A-V O_2 difference, but has a more variable effect on the nitrous oxide calculation for cerebral blood flow.

Discussion

The finding that intravenous nicotinic acid in flushing doses does not produce cerebral vasodilatation indicates that this drug probably has no place in the treatment of cerebral vascular disease unless it possesses some therapeutic action aside from its effect on cerebral vessels. No inferences can be drawn from these studies, however, concerning the effectiveness of nicotinic acid in the treatment of acute cerebral embolism in young persons, for no such subject was included in these observations. Our findings are in agreement with those of Loman, Rinkel, and Myerson,[7] who showed that intravenous nicotinic acid in doses of 100 to 150 mg. produced no significant changes in the cerebral arteriovenous oxygen difference in 4 cases and no changes in the cerebrospinal fluid pressure in 8 cases. They also showed that intracarotid nicotinic acid did not alter the cerebral arteriovenous oxygen difference. Our findings do not support the observations of Aring and his colleagues,[8] who found an increased intracranial blood flow following the administration of nicotinic acid. These workers used the method devised by Ferris[9] to measure relative intracranial blood flow; we feel that they did not measure the effect of nicotinic acid on the cerebral vessels, but rather on the vessels of the face. In this method, the skull is used as a type of plethysmograph, and changes in intracranial blood flow are measured by changes in the displacement of spinal fluid through a large needle in the lumbar region. A cuff is applied to the neck with sufficient pressure to prevent venous return from the head; the increased facial flow caused by nicotinic acid could have increased the pressure in the internal jugular system since the common facial vein enters into the internal jugular vein, and the venous return from the face is trapped by the cuff as effectively as the cerebral venous return. The only valves in the internal jugular vein are too far inferior to prevent this transmission of increased pressure into the internal jugular system and thence to the cerebrospinal fluid, thus producing an increased rate of spinal fluid displacement, due to increased facial blood flow, and not related to increased cerebral blood flow.

The observations presented here indicate that a significant amount of contamination of cerebral venous blood by blood from the face or neck, when vasodilatation in the face or neck has not been produced by heat or drugs, would result in a falsely low cerebral blood flow, A-V O_2 difference, and rate of O_2 consumption, and a falsely high cerebrovascular resistance. When vasodilatation in the face or neck has been produced, as by the administration of nicotinic acid, extracerebral contamination of cerebral venous blood may then result in a falsely high cerebral blood flow and a falsely low A-V O_2 difference. It is also demonstrated that nicotinic acid greatly increases the nitrous oxide content of the blood draining from the face and neck without altering the nitrous oxide content of cerebral venous blood, and therefore not altering cerebral blood flow.

The finding that the nitrous oxide content of blood draining from the external jugular vein (and hence the calculated flow through that vein) is not increased by a similar magnitude in different persons, whereas A-V O_2 difference is consistently and greatly decreased, is not explained by this study. It is possible that this variation of response by different individuals to nicotinic acid depends upon whether the increased blood flow to the tissues of the face and neck goes through capillaries or arteriovenous shunts. Increased capillary flow would allow the nitrous oxide to be absorbed by the tissues and yield a slower rise in the venous nitrous oxide curve than if arterial blood passed directly into the veins. It is also possible that

the individual characteristics of the tissues of the face and neck in different persons may influence the response of the venous nitrous oxide content to nicotinic acid. Finally, it is technically easier to measure changes in A-V O_2 difference than in blood flow, and this may well account for some of the disparity.

The consistently decreased A-V O_2 difference which results from the administration of nicotinic acid when extracerebral contamination is present offers a useful and simple test for determining the presence of extracerebral contamination in any subject. The patient can be given 50 to 100 mg. of nicotinic acid intravenously to produce flushing of the face, and then another sample can be drawn from the internal jugular bulb for oxygen analysis. If the oxygen content of the blood increases significantly, contamination has occurred. Certainly any observations on the effect of drugs on cerebral metabolism, as measured by the nitrous oxide method, should take into consideration the effects of the drug in question on the circulation in the face and neck.

These data also seem to indicate that extracerebral contamination of some degree is to be expected in about 20 per cent of the subjects studied by the nitrous oxide technic. Unless facial circulation is greatly increased, as by heat or drugs, the degree of contamination is probably quite small and should rarely affect a series of results.

Summary and Conclusions

1. Intravenous nicotinic acid in flushing doses produces no change in cerebral blood flow, arteriovenous oxygen and glucose difference, oxygen and glucose consumption, or vascular resistance.

2. The incidence of extracerebral contamination of cerebral venous blood in performing the nitrous oxide procedure for cerebral blood flow is thought to be around 20 per cent. This contamination is usually not of significant magnitude unless the facial circulation is increased by heat or drugs.

3. Significant contamination of cerebral venous blood by facial or neck blood in the resting subject at ordinary room temperature produces falsely low values for cerebral blood flow, A-V O_2 difference, and oxygen consumption by the nitrous oxide procedure. If contamination occurs when vasodilatation has been produced in the face and neck by nicotinic acid, a decreased A-V O_2 difference will consistently result, and also, in some cases, a falsely high value for cerebral blood flow.

4. For workers who use the nitrous oxide technic for measuring the effects of drugs on the cerebral circulation, a test for contamination of cerebral venous blood by extracerebral blood is suggested, using nicotinic acid as the testing substance.

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The Myocardium in Subacute Bacterial Endocarditis

By Otto Saphir, M.D., Louis N. Katz, M.D., and Ira Gore, M.D.

An evaluation of electrocardiographic tracings as an index of myocardial damage in survivors of subacute bacterial endocarditis was undertaken in a study of 76 fatal cases of the disease. Anatomic changes, present in all, included myocarditis, perivascular infiltration and fibrosis, Aschoff bodies, infarcts, and intravascular emboli. Electrocardiographic tracings revealed changes which could be attributed to myocardial impairment confirmed at autopsy. Variation of pattern in serial records, although not diagnostic of specific disease, indicated an active process within the myocardium. Correlation of the electrocardiographic tracings with pathologic changes was not complete, but was sufficiently close to demonstrate the diagnostic value of electrocardiograms.

SUBACUTE bacterial endocarditis, only a decade ago, was considered to be a progressive and almost inevitably fatal illness. The widespread use of penicillin and other antibiotic substances, however, has greatly altered the prognosis of this still serious disease. Recently, Rapaport and Ellis[1] were able to report 11 of 15 patients living and well more than two years after treatment. At the Michael Reese Hospital, Kaplan, Rosenman, Katz and Brams[2] found 15 out of 18 patients were alive twenty-five to forty-nine months after discharge from the hospital. Twelve of these were well; the other 3 suffered from congestive heart failure associated with free aortic valve regurgitation. These figures indicate that the antibiotics greatly increase the incidence of healing over that reported by Libman[3] more than a generation ago. Accordingly, it appears that greater clinical emphasis must be given the ravages and residua of the active infection than they have received in the past. In the heart these include not only the well recognized mechanical effects of the distorted and scarred valves, but also the impaired structure of the myocardium. No one will argue that the valvular system of a circulatory pump is more important than the propelling force itself.

Although Blumer[4] considered involvement of the myocardium to be slight and infrequent in subacute bacterial endocarditis, Libman and Friedberg[5] were cognizant of its frequent occurrence, but stated: "The myocardium shows a variety of lesions which are rarely as significant as in rheumatic fever unless there are concomitant active rheumatic lesions." They found Aschoff bodies in 25 to 45 per cent of the hearts examined microscopically, degenerative muscle changes in various stages of healing, and frequently, diffuse or localized collections of lymphocytes and mononuclear cells. It is unfortunate that in referring to such localized infiltrates, Libman and Friedberg chose to perpetuate the term Bracht-Wächter bodies.[6] None of the varying lesions produced experimentally by Bracht and Wächter[7] is characteristic of subacute bacterial endocarditis, and all of them may be found in myocarditis of varying etiology.[8–10]

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Materials and Methods

Although the character and incidence of the myocardial changes in subacute bacterial endocarditis have been adequately considered in the literature,[7, 11] it seemed timely to review them in correlation with the electrocardiogram; first, to test the reliability of the electrocardiogram as an index of myocardial damage in endocarditis lenta, and second, to ascertain whether the alterations observed followed any consistent pattern.

Among the many cases of subacute bacterial endocarditis in the files of the Armed Forces Institute of Pathology, 76 included adequate material for microscopic studies of the myocardium and electrocardiographic tracings. The series was made up of 11 females, all white, and 65 males, among them one Negro and one Indian. More than two-thirds of the group were less than 40 years of age at the time of death. The number of individuals in each decade are tabulated below.

Years	10–19	20–29	30–39	40–49	50–59	60–
Number	2	38	19	7	5	5

The study of the pathologic changes was limited by the amount and character of the material, which

consisted of routine sections of heart muscle sampled by the original prosector. Generally, in each case, two to four slides stained with hematoxylin and eosin were available; in a fair proportion, there were also slides prepared with Giemsa, Gram, and von Kossa stains. Had it been possible to examine multiple blocks of the myocardium, evidence of disease would no doubt have been much more frequent than in this or any other study of routine material. Similarly the electrocardiographic tracings were those taken at the discretion of the clinician whose interest lay in diagnosis and treatment rather than in the frequency with which transient alterations could be observed. The pathologic and electrocardiographic interpretations of this material were made independently to avoid the possibility that the findings in one would prejudice the evaluation of the other.

Discussion of Findings

Clinical Features

Though we are primarily concerned with the state of the myocardium, for statistical purposes it might be mentioned that the data in other respects did not vary from those accepted as usual in subacute bacterial endocarditis. Evidence of previous chronic disease was invariably present in the involved valve, but neither syphilitic nor congenital valvular disease was demonstrated. The culture data, which were incomplete, demonstrated *Streptococcus viridans* in 42 of the 76 cases, *Staphylococcus aureus* in 3, *enterococcus* in one and *meningococcus* in one. Treatment had included sulfa drugs in 27 cases and penicillin in 28. Unfortunately, the information was not sufficiently detailed to provide the basis for an opinion regarding the adequacy or efficacy of these antibiotic agents. Other therapeutic measures, symptomatic and supportive, consisted of the administration of sedatives and hypnotics, transfusions, and, not infrequently, digitalis. Historically, a clear-cut account of acute rheumatic fever had been elicited from 11 patients and that of chorea from one. The onset of the terminal illness followed acute upper respiratory infection in 8 instances, and dental extraction in 3. The autopsy disclosed chronic passive hyperemia of the viscera in 42 cases, frequently associated with hydrothorax, ascites and dependent edema, though failure of the heart was recognized clinically in only 27. Three patients died unexpectedly.

Microscopic Observations

The histologic alterations in the myocardium considered in relation to pathogenesis fall into general categories: (1) direct extension of the suppurative process from the affected valve into the adjacent heart muscle; (2) ischemic sequelae of vascular disturbances, such as embolization of coronary arteries and arterioles or localized endarteritis consequent to inflammation of the supporting cardiac tissues; (3) toxic changes manifested by parenchymatous degeneration of the type prominent in diphtheria, or interstitial infiltration as seen in myocarditis of various etiologies; (4) the effect of direct bacterial seeding and the resulting inflammatory reaction which infrequently leads to the formation of micro-abscesses; and finally (5) the residue of the predisposing heart disease. Of the last, only the Aschoff bodies have diagnostic significance. Scarring and fibrosis may represent late stages of any of the processes 1 through 4 enumerated above, as well as the end result of the primary process.

Table 1.—*Types of Myocardial Damage in Seventy-six Cases of Subacute Bacterial Endocarditis*

No. of Cases	Myocarditis	Perivascular		Aschoff Bodies	Infarcts	Emboli	
		Fibrosis	Infiltration			Bacterial or fibrin	Calcific
76	53	47	34	6	36	14	3

A.—*Number of cases showing combinations of myocardial lesions*

Myocarditis & Infarcts	Myocarditis & Perivascular Fibrosis	Myocarditis, Infarcts & Perivascular Fibrosis	Infarcts & Perivascular Fibrosis	Infarcts & Emboli	Myocarditis & Aschoff Bodies
25	25	11	7	11	5

B.—*Number of cases showing one lesion only*

Myocarditis	Perivascular Fibrosis	Infarcts
6	3	1

The morphologic types of myocardial damage are enumerated in the accompanying tables (1, 2, *A* and 2, *B*). Usually several varieties of

TABLE 2, A.—*Types of Myocardial Damage in Present Series*

AFIP ACC NUMBER	MYOCARDITIS	PERIVASCULAR CELLULAR INFILTRATION	PERIVASCULAR FIBROSIS	ASCHOFF BODIES	INFARCTS	CHRONIC PASSIVE HYPEREMIA	CEREBRAL EMBOLUS	ELECTROCARDIOGRAM
106583	0	0	+	0	+	0	0	Pre-existing left heart strain. No evolution, no progression.
106517	++	0	+	0	0	+	0	Evidence of old damage to the heart and recent evidence. Sinus tachycardia.
115368	+	0	+	0	+	0	+	Normal record. (EKG taken I day before death.)
123118	0	0	+	0	+	0	+	Low voltage, borderline curve.
126403	+	0	+	0	0	0	0	Inversion of T waves. P-R prolongation. Digitalis changes (?)
126919	+	+	0	0	0	+	0	Development axis shift. Premature auricular extrasystoles. T wave variation.
127425	+	+	0	0	0	+	+	ST depression, 2nd. degree A-V block. Ist. degree A-V block.
127434	0	+	0	0	0	0	0	Pre-existing heart disease. Low voltage. Mitral P wave. No recent involvement
127446	+	0	+	0	0	0	+	Sinus tachycardia, SD depression. T inversions. Low voltage.
127898	0	0	+	0	+	+	0	Sinus tachycardia, right axis shift. Tendency to low voltage. "Surprisingly normal record"
131794	+	0	0	0	0	0	0	Sinus tachycardia, Progressive changes compatible with myocarditis
131870	0	+	+	0	0	+	+	Sinus tachycardia. Progressive changes. Decrease in voltage.
132582	+	0	+	0	+	0	+	Definitely abnormal curve. Low voltage. Auricular fibrillation.
136682	0	+	+	0	0	0	0	Sinus tachycardia. Probably right heart strain. Abnormal record indicative of damage to the heart.
138935	0	+	+	0	+	+	0	Combined heart strain, auricular fibrillation. Premature ventricular systoles. Sinus rhythm was established on the day before death. 3 to 1 conduction.
139432	+	0	+	0	0	0	0	Sinus tachycardia, ventricular premature systoles with bigeminal rhythm. Low voltage. Note: Low voltage is theoretically explained with, and in this series is seen often with myocarditis.
140240	0	0	+	0	+	0	0	Sinus tachycardia, digitalis effect. Progressive development of left axis shift.
141398	+	+	0	0	0	+	0	Digitalis effect. T inversion. Sinus tachycardia. Right axis shift develops.
143125	+	0	0	0	+	0	0	Low voltage. Ist. degree A-V block. T inversion. Ventricular premature systoles.
143699	0	+	+	+	0	0	+	Sinus tachycardia.
147917	+	+	0	0	0	+	0	Sinus tachycardia. Digitalis effect. Development of right axis shift. Low voltage. (Note: digitalis effect obscures records.)
149855	+	+	+	0	0	+	0	T inversion. Sinus tachycardia— coronary-like pattern.
150908	+	+	0	0	+	0	+	Normal EKG.
159262	+	+	0	0	+	+	0	Inverted T waves. Tachycardia and changing EKG's, digitalis effect, tendency to low voltage. Ventricular premature systoles T inversion suggests coronary embolus.
159471	+	+	+	0	+	+	0	Low voltage. Sinus tachycardia, digitalis effect. Intraventricular block. Progressive left axis shift. Lengthening of the PR.
162404	0	0	+	0	0	0	0	Sinus tachycardia, digitalis, low voltage Q3.
168072	+	0	0	0	+	+	0	Low voltage, left heart strain. Tachycardia T inversion suggestive of involvement of the apical region in the heart. (sudden onset).
184469	0	0	+	0	+	+	0	Sinus tachycardia. Low voltage. Auricular premature systoles. Ist. degree A-V block. Progressive changes.
125136	+	0	+	0	+	+	0	Changes are suggestive of antero-lateral myocarditis or infarction. ST depressions. T inversions.
120070	+	0	+	0	0	+	+	Sinus tachycardia. Progressive changes. EKG changes.
116760	0	0	+	0	0	+	0	Ist. degree A-V block. Digitalis might explain the PR prolongation.
112051	+	0	+	0	+	+	+	Sinus tachycardia, low voltage. Ventricular premature systoles, digitalis contours. Almost complete A-V block. Changing EKG's.
169356	+	0	+	0	+	+	0	Ventricular premature systoles, multiple foci. A-V block. T inverted. Digitalis effect. Sinus tachycardia. Ist. degree A-V block. Temporary bigeminal rhythm.
109893	+	0	+	0	+	+	+	Sinus tachycardia, small T1 interpreted as borderline case.
108538	+	0	+	0	0	0	0	Normal EKG.
108600	+	+	+	0	+	+	0	T2 and T3 inverted. Low voltage. (after paroxysmal tachycardia).
156397	+	+	+	0	+	+	0	Low voltage. Continuous cardiographic changes indicative of progressive myocardial damage.
147205	+	0	+	+	0	0	+	Abnormal T waves with T2 and T3 inversion. Intermittent Wolf Parkinson White. T wave changes disappeared within a month. Premature systoles, nodal and ventricular bigeminal rhythm.
184586	+	+	+	0	+	+	0	Tachycardia, digitalis effect. No evidence of damage to myocardium.

TABLE 2, B.—*Types of Myocardial Damage in Present Series*

AFIP ACC. NUMBER	MYOCARDITIS	PERIVASCULAR CELLULAR INFILTRATION	PERIVASCULAR FIBROSIS	ASCHOFF BODIES	INFARCTS	CHRONIC PASSIVE HYPEREMIA	CEREBRAL EMBOLUS	ELECTROCARDIOGRAM
107211	0	+	+	0	0	0	0	Normal record
106151	0	0	+	0	0	0	0	Normal electrocardiograms
105321	+	0	0	0	0	+	+	Low voltage. Abnormal, compatible with myocarditis
101718	+	+	+	0	+	+	0	Changing electrocardiograms. Evidence of progression and healing. S-T changes. No atypical QRS complexes. Coronary-like pattern.
167166	0	+	+	0	+	+	0	Inverted T-waves. Progressive changes. Later digitalis changes.
167201	0	0	0	0	+	+	0	Sinus tachycardia. Pre-existing left heart strain and progressive changes.
167920	0	0	+	0	0	+	0	Tachycardia, progressive left axis shift. Low voltage. Progressive changes
168601	+	+	+	0	0	+	0	Low voltage Notching of P wave.
37488	+	0	0	0	+	0	+	Normal EKG
45210	+	0	0	0	+++	+	0	Sinus tachycardia, digitalis effect Mitral P waves.
52620	+	0	0	0	+	+	+	Normal EKG
52918	+	+	+	0	0	0	0	Intraventricular block. Q3. Ventricular premature systoles from multiple foci
65538	+	0	+	0	0	0	0	Sinus tachycardia, low voltage Abnormal curve which indicates damage.
70610	+	0	0	0	0	+	0	Low voltage Progressive changes. P. R prolonged.
71903	+	0	+	0	0	+	0	Auricular fibrillation. Mitral P wave, ventricular premature systoles, multiple foci. Digitalis changes Low voltage developed.
74134	+	0	0	+	0	+	+	Sinus tachycardia Low voltage.
74654	+	0	+	+	0	0	+	Normal EKG
80120	+	+	0	0	0	0	+	Sinus tachycardia, otherwise normal.
80219	0	0	+	0	0	+	0	Nodal rhythm in several of the records. Otherwise normal.
84734	+	+	0	0	0	+	+	Sinus tachycardia, low voltage.
85537	0	0	+	0	0	+	0	Tachycardia, low voltage, some evidence of digitalis.
90326	+	+	0	0	0	+	0	Nothing strikingly abnormal (record is continually changing).
90561	+	+	0	0	+	+	0	Mitral stenosis. Auricular fibrillation (note auricular fibrillation for 10 years with final subacute bacterial endocarditis).
92912	+	+	0	0	+	+	0	Three normal records. Taken 184 days before death.
93068	+	0	0	0	+	0	+	Ist. degree, AV block. Nodal premature systoles.
93432	+	+	+	0	0	0	+	Abnormal curve with small T waves.
94368	+	+	0	0	+	+	0	Low voltage, progressive changes.
94863	0	+	0	0	0	0	0	Low voltage. Progressive changes. P R prolonged.
96275	0	0	+	0	+	0	+	Tachycardia. T wave changes. S−T depressed
96507	+	+	+	0	0	+	0	Sinus tachycardia, abnormal record indicative of damage
96626	+	0	+	0	0	+	0	Sinus tachycardia, low voltage. Premature systoles nodal and ventricular
97558	0	+	0	0	++	0	+	Ist. degree A-V block.
98153	+	0	0	0	0	0	0	Sinus tachycardia Low voltage
98442	+	+	0	0	0	+	0	Normal EKG
102761	+	0	0	0	+	0	0	Digitalis effect Sinus tachycardia, low voltage
103616	+	+	0	0	+	0	0	First degree A-V block. ST depression
105208	0	0	+	0	+	+	0	Slight tachycardia

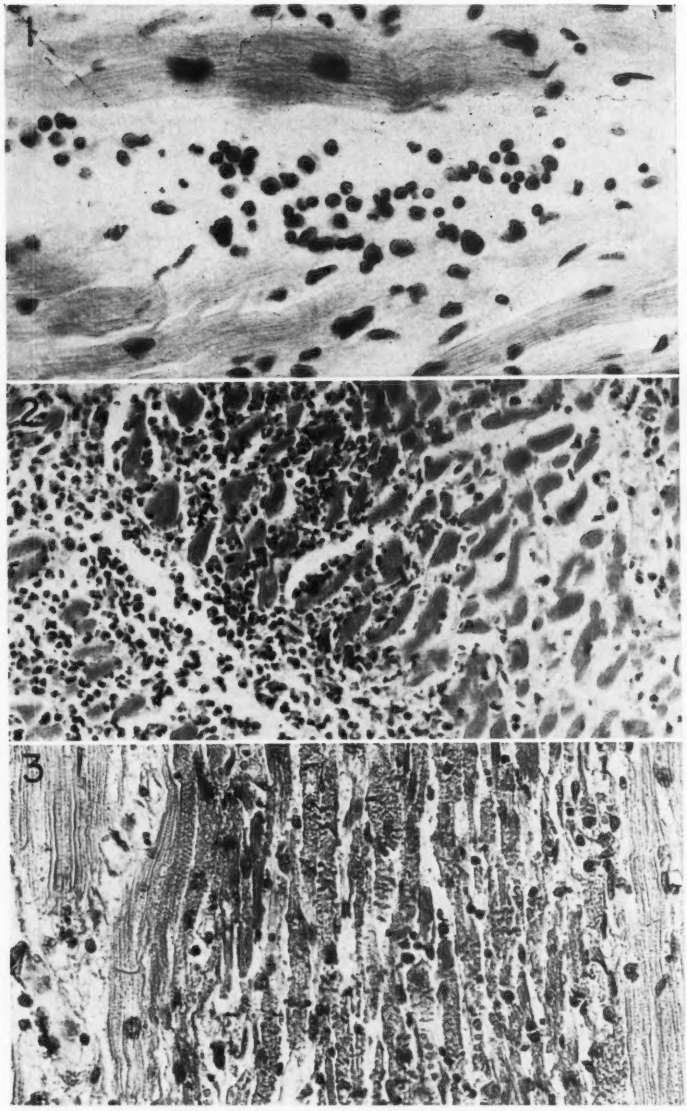

FIG. 1.—Myocardium exhibiting a focal area of interstitial infiltration by lymphocytic cells, macrophages, and granulocytes. AFIP Accession 126919. (Hematoxylin-eosin, × 235)

FIG. 2.—Phlegmonous type of myocarditis adjacent to a diseased valve. AFIP Accession 94368. (Hematoxylin-eosin, × 185)

FIG. 3.—A focal area of myocardial degeneration. Morphologically it is not always possible to ascertain whether such a change is toxic or ischemic. AFIP Accession 159471. (Hematoxylin-eosin, × 260)

change were to be observed (table 1, *A*, 2, *A* and 2, *B*) but a few hearts, as might be expected with limited sampling, presented only one type of histologic change (table 1, *B*). Not a single heart failed to show the presence of at least one of the lesions.

Myocarditis. The inflammatory infiltration other than that localized to perivascular areas

was usually focal but occasionally diffuse. Most often the process was interstitial with a preponderance of granulocytes, a fair proportion of lymphocytes, and a varying amount of edema (fig. 1). Diffuse myocarditis with prominent leukocytic reaction may be confused with early infarction but is to be distinguished by the slighter degree of muscle necrosis. Involvement of the muscle adjacent to the involved endocardium was often phlegmonous in character (fig. 2), and, since organisms identical with those in the vegetation could frequently be demonstrated, it represented a direct extension of the suppurative process. Usually, organisms were not demonstrable in more remote areas of the myocardium, and in these the myocarditis is presumed to have a toxic basis. In the presence of bacteremia it is possible that such lesions might arise from implantation of organisms which are subsequently destroyed by the body's defenses. Even that mechanism, however, is to be distinguished from the usual bacterial infection characterized by multiplication of the organism. The occurrence of similar histologic patterns in forms of myocarditis in which there is little reason to suspect the presence of circulating organisms lends weight to the view that at least some of the lesions of heart muscle in endocarditis lenta might have an analagous explanation. The type of myocarditis most frequently observed occurred without apparent relation to blood vessels and was characterized by an infiltrate primarily lymphocytic in nature.

Although much of the parenchymatous destruction observed in these hearts was secondary to vascular alterations, it seems likely that some of it, at least, was a toxic effect (fig. 3). At any rate, small foci of acute muscle necrosis were occasionally seen which differed from the type resulting from ischemia in failing to exhibit (1) the usually striking granulocytic reaction, (2) necrosis of the stromal cells, and (3) prompt karyolysis. In such areas, in contrast to infarction, the cytoplasmic components of the muscle fibers had suffered much more degenerative change than had their nuclei.

Microabscesses were infrequently observed but were considered to be clearly the result of bacterial implants (fig. 4). Sharply localized and tightly packed interstitial accumulations of polymorphonuclear leukocytes, unassociated with necrosis, were similarly regarded as an effect of hematogenous seeding. Although lesions of the latter type necessarily preceded the formation of microabscesses, they did not go on to suppuration.

Perivascular cellular infiltration was a common lesion, having been observed in 34 instances (fig. 5). Cytologically, its character was identical with interstitial myocarditis, and in fact the two disorders were most commonly found together. Pathologists faced with the problem of establishing the etiology of certain forms of chronic heart disease have in general followed the lead of Gross and co-workers[12] in accepting perivascular fibrosis in the heart as evidence of a previous rheumatic carditis.[13] Inasmuch as fibrosis may eventuate as readily from a nonspecific inflammation as from the rheumatic variety, it seemed appropriate to note how frequently the process was perivascular, by way of emphasizing that the microscopic picture alone is inadequate to permit unequivocal acceptance of lesions of this variety as rheumatic "stigmata." Though it is true that many of the 48 instances of perivascular scarring observed in the study may have been the residue of previous myocardial disease, there were also sufficient transition stages between the nonspecific inflammatory process and fibrosis to lead to the conviction that many such lesions had developed during the course of the terminal illness. Occasionally the vessel included within the lesion exhibited a mild degree of endothelial proliferation. The phenomenon is nonspecific since obliterative changes are to be observed in other anatomic sites whenever a vessel traverses an inflammatory zone. In the heart, however, the end-artery character of the circulation makes these vascular lesions significant, especially since the vessels affected are of the caliber of those from which the physiologic anastomoses develop with increasing age.[14]

With rather strict criteria used for the histologic identification of the Aschoff nodule, active rheumatic lesions were found in only 6 hearts. All hearts bearing Aschoff nodules were from one or another of the 11 patients who had

given a medical history of a clear-cut clinical attack of rheumatic fever. Other reports[5, 7, 15] indicate that the true incidence of rheumatic

gone early organization (fig. 6). The presence of older well-vascularized infarcts and fibrous scars replacing portions of the myocardium

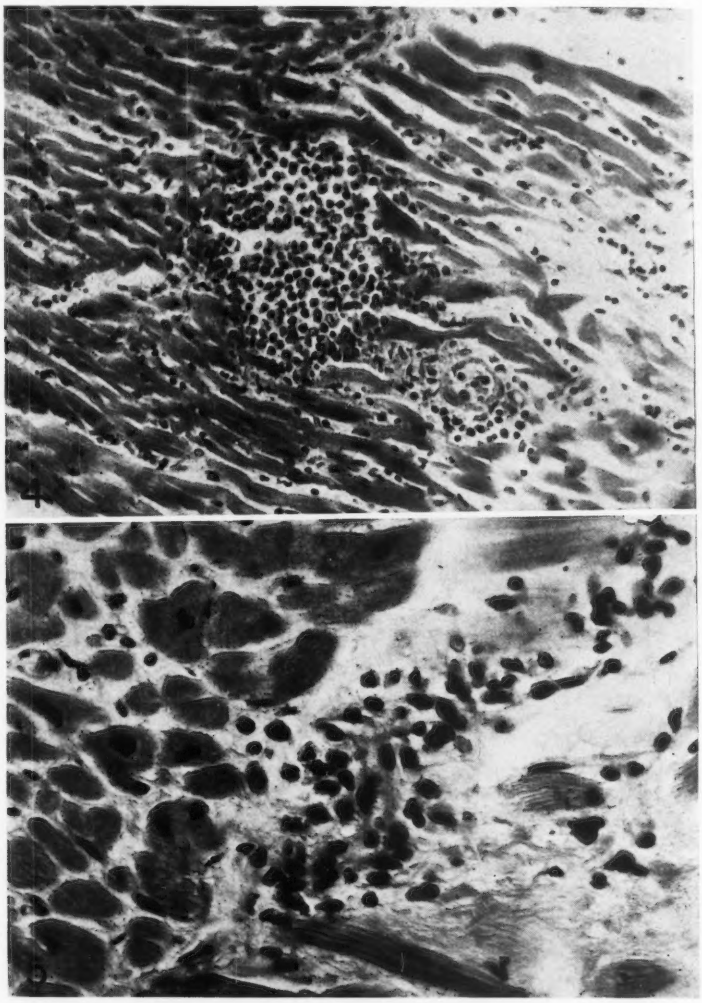

FIG. 4.—Micro-abscess within the myocardium. AFIP Accession 106517. (Hematoxylin-eosin, × 185)

FIG. 5.—Circumscribed perivascular infiltration predominantly mononuclear in character. AFIP Accession 132582-2. (Hematoxylin-eosin, × 235)

activity in subacute bacterial endocarditis ranges between 25 and 45 per cent.

In somewhat fewer than half the cases myocardial lesions of ischemic character were found. Most often they were microscopic in size and usually they were sufficiently old to have under-

would indicate repeated insults during the course of the disease (fig. 7). Multiplicity of infarcts was the rule. The infrequency of recent infarction presumably demonstrates that the approach of death had not been associated with an acceleration of the process producing

the lesion. Occasionally, freshly necrotic fibers were noted to have become incrusted with calcium, iron, or both calcium and iron; a rather unusual manifestation.[16]

shown would be revised upward had the heart muscles been sampled more liberally. Obliterative vascular changes in a coronary vessel traversing an inflammatory focus, as previously

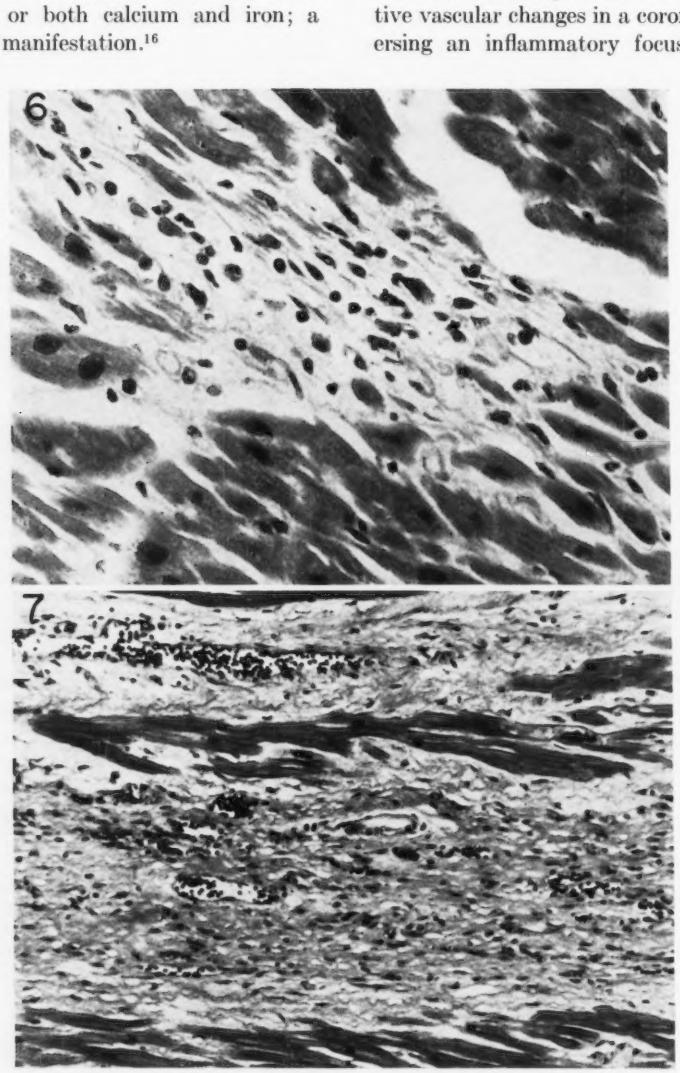

FIG. 6.—Micro-infarct of myocardium undergoing organization. AFIP Accession 103517-3. (Hematoxylin-eosin, × 210)

FIG. 7.–Relatively large focal area of myocardial fibrosis interpreted as an organized infarct. AFIP Accession 109839. (Hematoxylin-eosin, × 135)

The most obvious basis for the development of ischemic necrosis was the occurrence of coronary embolization. Emboli were found in 17 of the 36 hearts presenting infarctive changes, an incidence which previous studies[17] have

mentioned, may also occur and contribute, in some degree at least, to the formation of infarcts. The vessels involved were, as a rule, the smaller branches of the coronary arteries; though embolization of a major coronary artery

may occur and has been reported (figs. 8 and 9). The minute size of the infarcts generally found reflects the smaller caliber of the occluded vessel.

The composition of the emboli occurring in subacute bacterial endocarditis indicated their origin from the valvular vegetation[17]; in 14 instances they were fibrinous and usually contained a few granulocytes, though exceptionally polymorphonuclear leukocytes formed the bulk of the structure. Sometimes a ring of leukocytes surrounded the occluded vessel; occasionally the suppurative process had spread into the adjacent tissues.

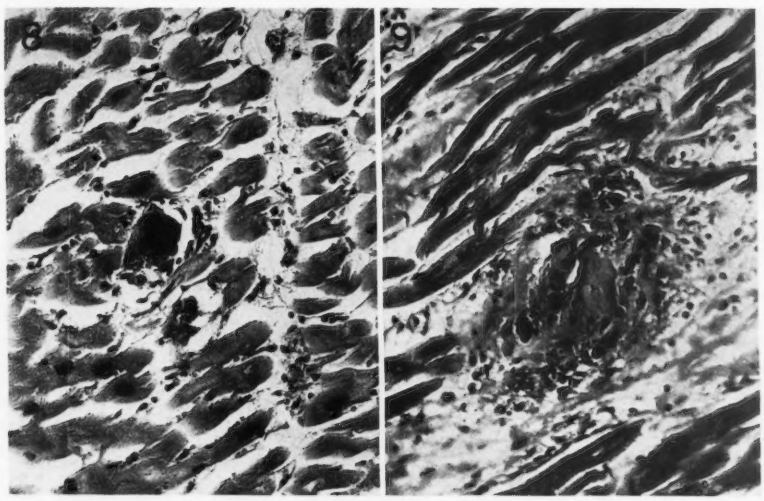

FIG. 8.—Embolus in a small intramyocardial vessel. AFIP Accession 148474-1. (Hematoxylin-eosin, × 210)

FIG. 9.—Intravascular embolus with surrounding reactive changes. AFIP Accession 101067. (Hematoxylin-eosin, × 175)

Electrocardiographic Findings

Electrocardiographic tracings taken during the terminal illness were available in the 76 cases studied pathologically. In most instances they were made sufficiently close to the date of death to support the premise that much of the anatomic change observed post mortem had very likely been present at the time of the tracing. However, in a study based purely on the routine electrocardiograms requested by the clinician, certain deficiencies are to be noted. The proper time relations were not always fulfilled; there were, in many instances, insufficient seriatim records; chest leads were not always available; many of the patients had received digitalis and occasionally quinidine. Specific patterns attributable to the drug were recognized in 22 instances, but it is not unlikely that some of the nonspecific effects noted among the others may also have been due to digitalis. Furthermore, in many cases it was apparent that the pre-existing heart disease, which was the background for the subacute bacterial endocarditis, produced abnormalities in the record. Without tracings before the onset of subacute bacterial endocarditis, it is difficult to judge to what extent the observed alterations are properly attributable to the final illness. Despite these limitations, certain information is to be derived from the analysis.

In 33 of the 76 cases, low voltage occurred, and in many instances it was seen to develop in serial tracings. This finding in 44 per cent of the cases is significantly frequent. In our experience,[18] low voltage accompanies those forms of heart disease associated with diffuse involvement, an impression which was sub-

stantially supported by the demonstrated myocardial lesions in subacute bacterial endocarditis.

Axis shifts occurred to the left in 36 cases (including one instance of possible left heart strain), and to the right in 20 instances (including 2 instances of possible right-sided heart strain). No axis deviation occurred in 17 cases and in one case the electrical axis shifted from the left to the right. No diagnostic or prognostic import can be attached to the axis deviations since they are normal variants. There were no examples of true heart strain properly attributable to the terminal heart disease. One instance of right-sided heart strain and 2 involving the left side were due to pre-existing disease. There were 4 questionable instances of heart strain, 2 affecting the right and 2 the left side of the heart.

The electrocardiographic tracings revealed a coronary pattern in 12 instances. Five were of the anterior type, 2 posterior, one lateral and 3 atypical. The changes were confined to the ST-T complex and in this respect the recordings varied from the typical in not showing the classic QRS disturbances. In several instances there were evolutionary changes in serial recordings. In only 8 of these cases did the coronary pattern appear to be directly related to the subacute bacterial endocarditis; in 2 others it was due to pre-existing coronary disease and in one it represented a post-tachycardial syndrome. Electrocardiographic tracings resembling those in coronary disease are not infrequently obtained in myocarditis of varied etiology, and therefore it is not surprising to find similar patterns in 12 per cent of the cases of subacute bacterial endocarditis. It must be pointed out that ST-T changes are an expression only of the injury currents of living muscle and can not be presumed to indicate the pathologic nature of the injury, whether it be ischemic, toxic, or traumatic. Nevertheless, it is somewhat disappointing that a higher incidence of this electrocardiographic abnormality was not found since, pathologically, myocardial infarcts were demonstrated in almost half of the cases. Perhaps their usually microscopic size and wide dissemination account for the discrepancy.

In an analysis of abnormalities of individual complexes, notched P waves were found 6 times. (In one instance this was due to pre-existing rheumatic heart disease.) Two other instances of P-wave abnormality were encountered, one of these being a P pulmonale, the other nonspecific. The only significant QRS change was the low voltage already mentioned in 33 cases. Depression of the S-T segment occurred in 35 instances and diphasic or inverted T waves in a like number. In some instances depression of the S-T segment was associated with T-wave inversion. Thus, in 45 of the 76 cases there were S-T depressions and/or inversion of the T wave. While 22 of these abnormalities might be attributed to digitalis and 4 others to pre-existing disease, in the remaining 19 there was no cause other than the subacute bacterial endocarditis. Finally, small T waves were seen in 10 instances, 7 of which presented no other change. In summary, it is apparent that abnormality of the ST-T complex is the most common one in subacute bacterial endocarditis, that closely following it in frequency is low voltage, and that abnormal P waves are relatively infrequent.

Abnormalities of rhythm or conduction disturbances occurred frequently. Sinus tachycardia was encountered in 40 of the 76 cases. It may be interpreted variously as an effect of fever, intoxication, or as a compensatory mechanism to the impaired contractile power of the heart in myocarditis. Paroxysmal tachycardia found twice was of ventricular origin in one and supraventricular in the other. There were 23 instances of ectopic rhythm, 7 of which were of the multiple variety. Premature systole was the rhythmic disorder most often observed and was of ventricular origin in 16 cases, auricular in 3, and nodal in 3. In 7, the extrasystoles originated from multiple foci. Bigeminal rhythm was encountered in 5 cases but was persistent in only one. There were 3 cases of auricular fibrillation, but one was obviously due to pre-existing disease. The single instance of auricular flutter was also due to pre-existing disease. Finally, there was one clear instance of the Wolff-Parkinson-White syndrome, another of passive nodal rhythm which might possibly have been a Wolff-Parkinson-White syndrome.

and a third in which there had been wandering of the pacemaker to the A-V node. The multiplicity of myocardial lesions observed correlates well with the numerous instances of active ectopic rhythm.

Auriculo-ventricular conduction delay was observed in 12 instances; in one additional case the P-R interval lengthened progressively, though it was still within normal limits. In 7 terminal illness twice, to quinidine once, and to pre-existing disease in the final instance. There is, therefore, a remarkably high incidence of abnormalities (54) of impulse origin and conduction in these 76 cases; a circumstance which finds its explanation in the frequency and multiplicity of the anatomic lesions.

Serial records were available in 61 cases, the remaining cases had only single tracings. Of

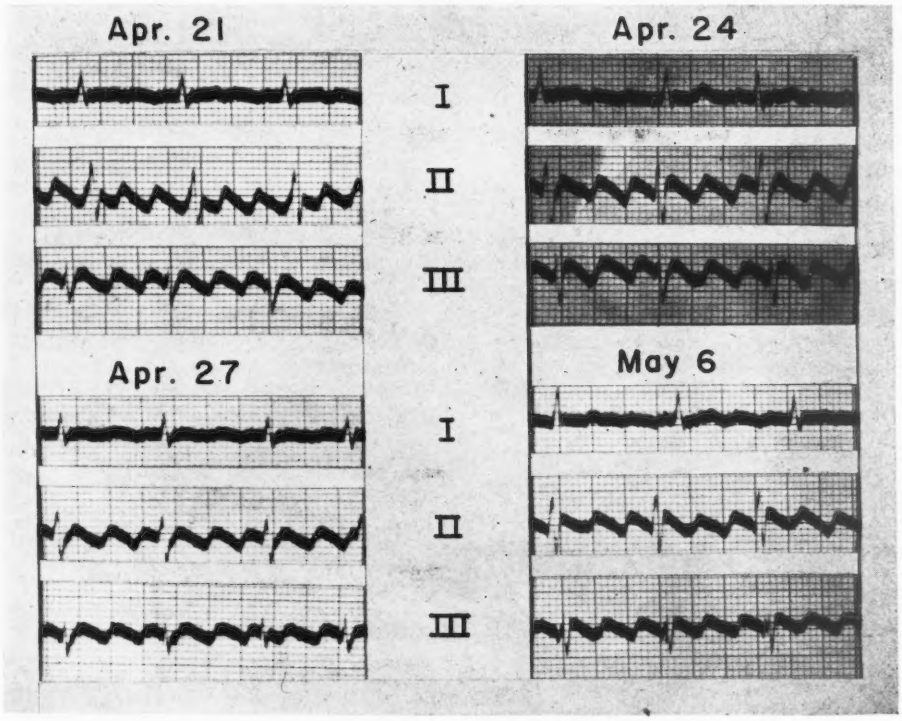

FIG. 10.—Four records of limb leads to illustrate a persistent 3:1 auricular flutter. This occurred independently of the subacute bacterial endocarditis and is presented only because of the rarity of a mechanism of a 3:1 conduction. AFIP Accession 138935.

of these (one being due to pre-existing disease) the block was of the first degree; in 2 it fluctuated between first and second degree; it varied between second degree and complete in one; it was almost complete once, and complete in one. While digitalis may have contributed to delayed conduction in some instances, it was apparent that it was often due to the disease process itself. Intraventricular block was encountered in 4 cases and was attributed to the

those in which serial studies were possible, 46 (75 per cent) showed significant and progressive changes in contour (figs. 10, 11 and 12). It seems reasonable to conclude, therefore, than an unstable electrocardiographic contour is an expression of involvement of the heart. While this, like the other changes described, can not be considered diagnostic of subacute bacterial endocarditis, it indicates an active injurious process within the myocardium and, in that

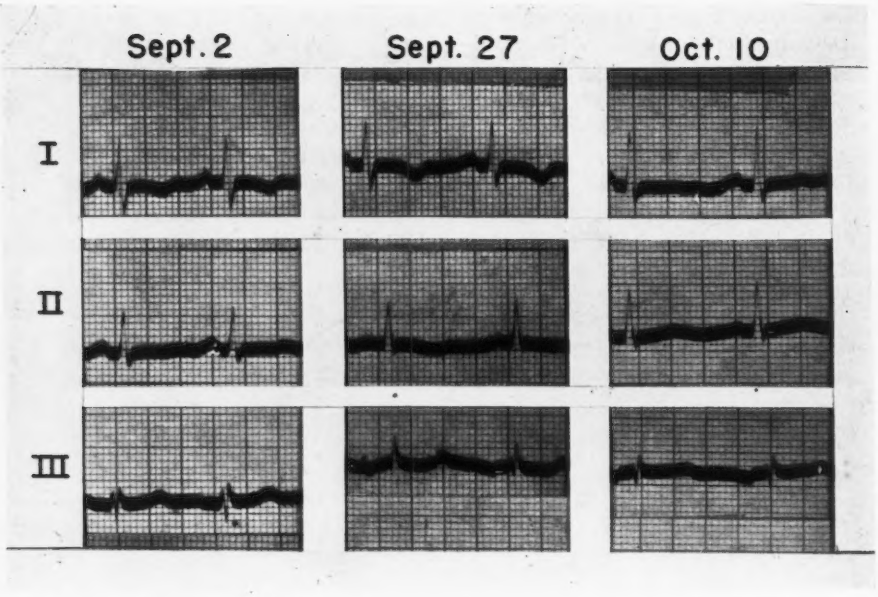

FIG. 11.—Three successive electrocardiograms taken on a patient approximately eleven months before death in whom necropsy revealed besides the subacute bacterial endocarditis, myocarditis, perivascular infiltrations and minute infarcts. Note the abnormally inverted T wave in Leads I and II which changed in the successive records, as well as other minor variations in P and QRS contour. AFIP Accession 101718.

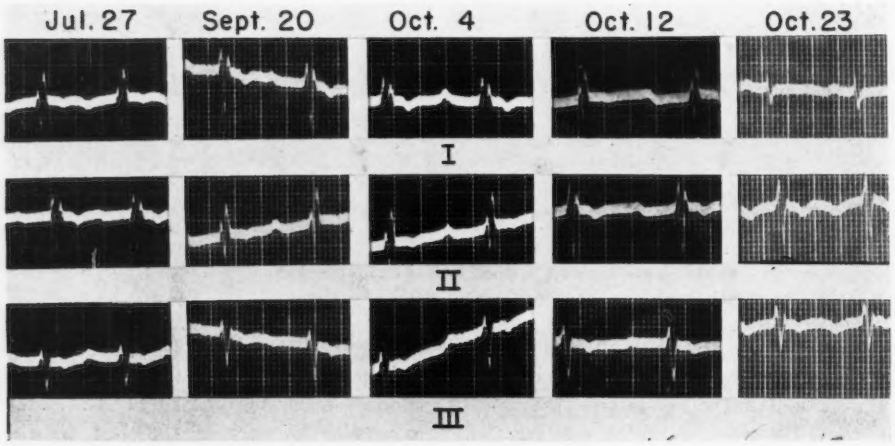

FIG. 12.—A series of records taken 4 months prior to death. Necropsy revealed subacute bacterial endocarditis with myocarditis, perivascular infiltrations, minute infarcts and small coronary emboli. The first record is within normal limits. Note the marked changes in the T wave in the subsequent records consisting in the appearance of a polyphasic QRS in Lead III and small inverted T waves in Leads I and II which wax and wane. AFIP Accession 125136.

sense, may have diagnostic value. Furthermore, the progressive character of the changes observed in these fatal cases may have prognostic significance, but this point requires verification by comparison with cases of arrested or healed subacute bacterial endocarditis.

Finally, on integrating the electrocardiographic findings tabulated briefly in tables 2, *A* and 1, *B*, and using the criteria employed at the Michael Reese Hospital[18] as to their normality, 56 cases (74 per cent) presented abnormalities, the records were borderline in an additional 7, and normal in only 11. In the remaining cases, the only available record in one was obtained before the onset of subacute bacterial endocarditis, and in the other the records showed sinus tachycardia.

Summary and Conclusion

For purposes of correlating the myocardial changes with the electrocardiographic tracings, a review was made of the material in 76 fatal cases of subacute bacterial endocarditis filed at the Armed Forces Institute of Pathology. Anatomic changes were present in all cases and consisted of myocarditis, perivascular infiltrations and fibrosis, Aschoff bodies, infarcts, and intravascular emboli. In most instances the myocardium contained combinations of these lesions.

The electrocardiogram revealed changes in contour and rhythm (the former showing evolution in seriatum curves) which could be attributed to the damage of the myocardium expected in subacute bacterial endocarditis and which were confirmed at necropsy. While correlation with the post-mortem lesions was not complete, it was sufficiently close to suggest that the electrocardiogram could be a valuable index of the presence of myocardial lesions. If such a deduction is justified from an examination of electrical tracings, it follows that similar evaluations of other clinical findings might likewise be informative. It would be advantageous for the physician to seek out clinical evidence pointing to the presence of myocarditis. Failure to detect it clinically is, in many instances, due to the fact that the possibility has not been considered. The greatly increased survival rate since the introduction of antibiotics endows such considerations with more than academic interest.

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Review of Single Coronary Artery with Report of 2 Cases

By JOHN CHANDLER SMITH, M.D.

The paper includes a discussion of all published cases of single coronary artery and a consideration of the embryologic development and physiologic significance of this anomaly. The incidence and types of associated cardiac diseases are reviewed. Two additional case reports of this anomaly are included.

THE OCCURRENCE of a single coronary artery is such a rare cardiac anomaly that presentation of 2 additional cases is of interest. The first case is unique in that the patient was the oldest in whom such an anomaly has been reported. In addition, pertinent data on 43 previously reported cases are presented.

CASE REPORTS

Case 1.—The patient was a white woman, 80 years of age, who entered University Hospitals of Cleveland with complaints of constipation and severe nausea for the past twenty-four hours and sharp attacks of pain over the lower abdomen of twelve hours' duration. She had never experienced chest pain, shortness of breath or edema of the ankles. Physical examination revealed a firm mass in the rectum and a sigmoid colostomy was performed on the day of hospital admission. On the thirteenth hospital day an abdominoperineal resection was performed and examination of the specimen disclosed a partially differentiated adenocarcinoma of the rectum. Metastases were not found. Edema of the legs and ankles developed on the fourth hospital day. The patient became comatose and died on the eleventh hospital day.

Autopsy (No. 15031): The heart weighed 340 grams. The epicardium was smooth and glistening. The muscle of the ventricles was uniformly brownish red and moderately firm throughout. The endocardium was smooth and glistening except over the posterior wall of the left atrium where there was a poorly demarcated focus of fine wrinkling. The leaflets of the mitral valve were slightly thickened and opaque along the free border. The cusps of the aortic valve were smooth and pliable and revealed moderate subcommissural adhesions.

A saccular dilatation, 0.6 cm. in diameter, was present in the wall of the right aortic sinus at the normal site of origin of the right coronary artery. A single coronary artery originated from the left aortic sinus and divided into an anterior descending and a circumflex branch. The former divided once and both branches extended obliquely over the anterior surface of the left ventricle, the larger continuing to the apex where it could be followed over the posterior surface of the left ventricle for 2 cm. Cross sections of the first portion of the larger anterior descending branch revealed yellowish gray intimal plaques that nearly occluded the lumen. The circumflex branch of the left coronary artery extended around the posterior surface of the left ventricle along the atrioventricular groove to the acute margin of the heart and continued to the anterior surface of the right ventricle to the base of the right auricular appendage. The course of this vessel measured 25 cm. from aortic orifice to the base of the right auricular appendage (fig. 1). Cross sections revealed a patent lumen throughout with slight focal thickening of the intima by yellowish gray plaques. Small branches extended over the posterior surface of both ventricles and over the anterior surface of the right ventricle.

Histologic examination of the myocardium revealed moderately large muscle fibers with nuclei that were slightly enlarged and occasionally rectangular. The myocardium was not otherwise remarkable. Histologic sections of the first portion of the larger branch of the left anterior descending coronary artery revealed marked thickening of the intima and subintimal deposition of a large amount of eosinophilic material containing acicular spaces. The lumen was reduced to a slit.

The pathologic diagnoses included recent abdominoperineal resection for partially differentiated adenocarcinoma of the rectum, acute fibrino-purulent peritonitis, recent sigmoid colostomy and abscess of the anterior abdominal wall. There was a single left coronary artery. In addition, there were healed nondeforming endocarditis of the mitral and aortic valves, bronchopneumonia of the right and left lungs, chronic cholecystitis with cholelithiasis and slight arteriolar nephrosclerosis.

Case 2.—The patient was a white woman 66 years of age who entered University Hospitals of Cleveland with complaints of lethargy, slurring of speech and weakness of the left arm of two days' duration. She had been diabetic for the past eight years and had been treated with 15 units of insulin daily. There had been no chest pain, ankle edema or shortness of breath.

From the Institute of Pathology, Western Reserve University Hospitals, Cleveland, Ohio.

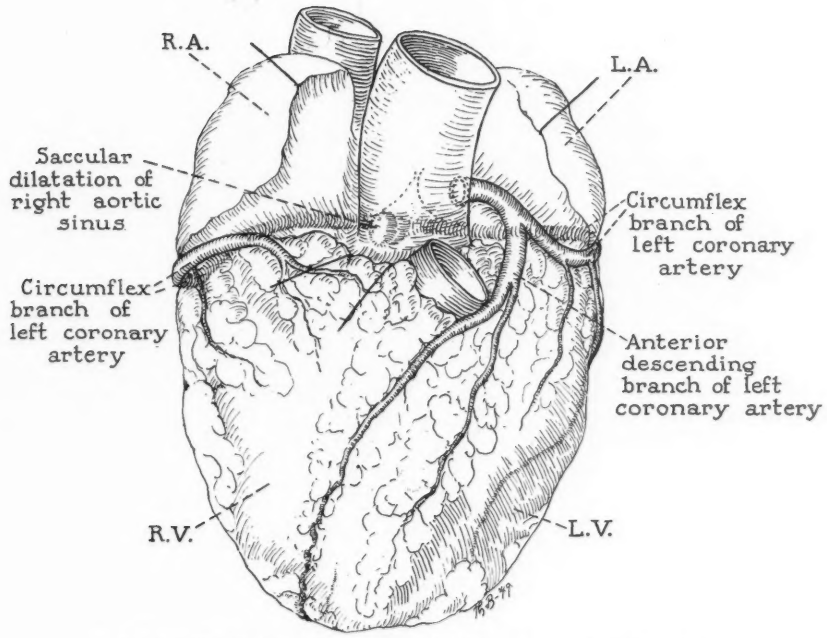

FIG. 1.—The distribution of the single left coronary artery of Case 1.

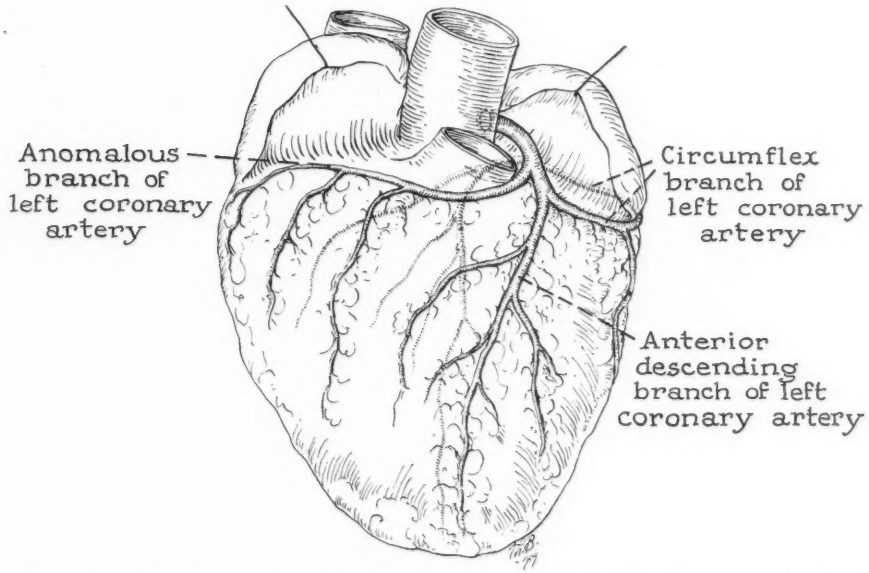

FIG. 2.—The distribution of the single left coronary artery of Case 2 with an anomalous branch extending to the right ventricle.

Urinalysis revealed 4 plus sugar, 4 plus acetone and 3 plus di-acetic acid. The blood sugar was 224 mg. per 100 cc. and the carbon dioxide combining power of the plasma was 58 volumes per cent.

Intravenous infusion of 5 per cent glucose in normal saline with 35 units of regular insulin was given. Small doses of insulin were given throughout the night and by the second hospital day the urine was free of acetone. However, the temperature gradually rose to 40 C. and the patient died on the third hospital day.

Autopsy (No. 8022): The heart weighed 250 grams. The epicardium was smooth and glistening. The myocardium was moderately firm and light brownish red throughout. The free margins of the tricuspid and mitral valves were thickened and opaque. There were slight subcommissural adhesions between the cusps of the aortic valve. The endocardium was smooth and glistening except over the posterior wall of the left atrium where there was a focus of fine wrinkling and gray opacity.

A single coronary artery originated from the left aortic sinus and divided into an anterior descending branch and a circumflex branch. Approximately 1 cm. from the origin of this single coronary artery, a moderately large branch extended to the right, passing anterior to the pulmonary conus to be distributed over the anterior and lateral surfaces of the right ventricle (fig. 2). The circumflex branch extended around the atrio-ventricular fold to send a branch down the obtuse margin of the left ventricle and a branch down the posterior surface of the interventricular septum. From the latter, small branches extended to the posterior surface of the right ventricle. Cross sections revealed yellow intramural deposits that encroached moderately on the lumens of all of these arteries.

Microscopic examination of the myocardium revealed oval nuclei within the muscle fibers. Foci of fibrosis were not seen. Histologic sections of the coronary arteries revealed needle-shaped spaces within subintimal depositions of eosinophilic material that encroached moderately upon the lumens. There was a large amount of glycogen within the epithelial cells of the renal tubules. There was moderate fat infiltration and marked atrophy and interstitial fibrosis of the pancreas.

The pathologic diagnoses included moderate arteriosclerosis of a single left coronary artery, bronchopneumonia of the right and left lungs, pronounced fibrosis and atrophy of the pancreas, moderate arteriolar nephrosclerosis and acute hemorrhagic cystitis.

Discussion

According to Banchi,[1] a case of single coronary artery was reported by Thebesius[2] in 1716. In 1827, Mayer[3] described, as an incidental anomaly in a fetus of 7 months' gestation with cor biloculare, a single coronary artery that arose from the right carotid artery and extended to the heart to divide into two branches to supply the myocardium. Since 1716, 43 cases have been reported. With the 2 cases here described, a total of 45 cases of single coronary artery is now on record.

The definition of a heart with a single coronary artery is one in which the entire myocardium is nourished by an artery, regardless of distribution, that arises by one ostium from an arterial trunk. In all but 2 of the cases thus far reported, the single coronary artery has arisen from the aorta. The case of Mayer[3] is mentioned above. In the case of Tow,[28] examination of a white female infant, 5 months old, revealed a cor biloculare with a single vessel arising from the pulmonary artery that divided into two branches to supply the myocardium. No arteries issued from the ascending aorta. In the case of Forester,[5] examination of a newborn white male infant revealed no arteries originating from the sinuses of Valsalva but a single coronary artery arising from the inferior aspect of the arch of the aorta. In all other reported cases the single vessel has arisen from the aorta within one of the sinuses of Valsalva.

According to the definition of single coronary artery here set down, the following cases, although included in other reviews, have been omitted here. The case of Grätzer[32] and the case of Sanes[33] are excluded because, in each, three separate coronary arteries issued from a single aortic sinus. The case of Bland, White and Garland[34] is also excluded because 2 closely adjacent coronary arteries arose from the same aortic sinus. The 21 cases reviewed by Soloff[35] are not included because in each the heart was supplied by two coronary arteries although one or both arose from the pulmonary artery.

With these deletions, the literature embodies 43 acceptable cases of single coronary artery. Because of embryologic considerations relative to the formation of this anomaly, these cases are conveniently classified into three types according to the distribution of the single coronary artery. The first type includes those cases in which the single vessel follows the course of only the normal right or left coronary artery. This type is illustrated in figure 1 and the 10 reported cases of this type are assembled in table 1. The second type of single coronary

artery includes those cases in which the single vessel arises by one ostium but divides so that branches are present in the distribution of both the right and left coronary arteries. This distribution is illustrated in figure 2 and the 17 cases of this type are assembled according to patient age in table 2. In 1938, Krumbhaar and Ehrich[26] included as a group those cases of single coronary artery in which the distribution of the vessel was so atypical that it could not be compared in this regard with either the right or the left coronary artery. The 12 cases of this type are assembled in table 3. Also included in table 3 are 3 cases in which insufficient data regarding distribution of the single vessel precludes consideration in tables 1 or 2.

Consideration of embryologic development of normal coronary arteries clarifies proposed mechanisms of formation of this anomaly. The first indications of the coronary arteries in rabbits appear as thickenings of the aortic endothelium in embryos of 10 mm. length.[36] This occurs just before division of the truncus communis into aorta and pulmonary artery by growth of the endocardial cushions. The arterial rudiments are at first solid columns of cells which later acquire a lumen and grow outward into the superficial portion of the myocardium. Both arteries pass at first to the bulbus cordis and then spread out over the heart, uniting with the capillary network and intertrabecular spaces in the developing myocardium. According to Grant,[37] the same description of development applies to the human heart.

Most authors agree that the majority of cases of single coronary artery are caused by one of two developmental anomalies. The first is a congenital absence of one coronary artery anlage. In cases presumably of this type, assembled in table 1, the single vessel follows the normal course of the artery it represents. In 1882, Hyrtl[38] stated that cases of absent coronary artery were limited to examples of this type. It was his opinion that cases in which one artery supplied the heart in the distribution of both normal right and left coronary arteries were examples of misplacement rather that absence of one coronary artery anlage. Other authors,[27, 31, 33] however, suggested that in the absence of one coronary artery, the remaining vessel might develop compensatory branches that would follow the course of the missing vessel and act as functional substitutes. As both of these suggestions are tenable, and neither has been disproved, the distribution of the single vessel cannot

TABLE 1.—*Single Artery Present in the Distribution of Only One Coronary Artery (Fig. 1)*

No.	Age	Sex	Single Artery Present*	Weight of Heart	Autopsy	Year	Author
				grams			
1.	4 days	M	L	30	Truncus solitarius	1930	Shapiro[16]
2.	33 years	M	L	520	Cerebral hemorrhage	1930	Petren[17]
3.	35 years	M	L	—	Dissecting aortic aneurysm†	1947	Roberts and Loube[31] (case 7)
4.	37 years	M	L	—	Subacute bacterial endocarditis†	1922	Plaut[12]
5.	39 years	M	L	—	Pneumonia	1935	Kochel[20]
6.	42 years	F	L	430	Rheumatic myocarditis	1940	Maddox and Ibister[29]
7.	44 years	F	L	400	Pulmonary embolus†	1938	Krumbhaar and Ehrich[26] (case 1)
8.	45 years	M	R	480	Lobar pneumonia	1940	King[30]
9.	63 years	M	L	150	Carcinoma of stomach	1937	Richter[25] (case 1)
10.	66 years	F	L	340	Carcinoma of colon	1947	Geever and Ravin[24]

* Left or right side.

† In addition to the diagnoses listed, there was a saccular dilatation of the aortic sinus from which the missing coronary artery normally arises.

be used as a criterion to distinguish absence from misplacement of one coronary artery anlage.

The second developmental defect accepted as a cause of single coronary artery is misplacement of one coronary artery anlage so that this anlage fuses with the first portion of the all authors recognize that cases of single coronary artery are examples of misplaced coronary anlagen and that the essential lesion is not an absence of the vascular supply. Krumbhaar and Ehrich[26] had no way of deciding whether the anlage was absent or misplaced but stated that the small saccular dilatation of the aortic

TABLE 2.—*Single Artery Present in the Distribution of Both Coronary Arteries (Fig. 2)*

No.	Age	Sex	Single Artery Present*	Weight of Heart	Autopsy	Year	Author
				grams			
1.	Fetus, 7 months	—	L	—	Thoracopagus	1841	Hyrtl[38]
2.	100 days	F	R	—	Anomaly of heart†	1935	Ngai[22]
3.	35 years	M	R	450	—	1933	Born[19] (Case 2)
4.	35 years	F	R	285	Carcinomatosis	1938	Krumbhaar and Ehrich[26] (case 2)
5.	37 years	M	—	—	Hemopericardium	1947	Roberts and Loube[31] (case 6)
6.	39 years	F	L	Enlarged	Pulmonary tuberculosis	1909	Garand[10]
7.	40 years	M	L	240	Malignant hemangioma of lungs‡	1935	Hall[23]
8.	42 years	M	L	—	Pulmonary tuberculosis	1947	Roberts and Loube[31] (case 2)
9.	45 years	F	R	—	Chronic mitral and aortic valvulitis	1925	Gallavardin and Ravault[14]
10.	46 years	M	R	930	Thrombus of coronary artery, recent infarct of myocardium	1926	Smith and Graber[15]
11.	46 years	M	R	—	Old infarct of left ventricle	1947	Roberts and Loube[31] (case 4)
12.	54 years	M	R	750	Pneumonia and empyema	1933	Born[19] (case 1)
13.	60 years	F	R	—	Chronic mitral and aortic valvulitis	1867	Bochdalek[7]
14.	61 years	M	R	475	Cerebral hemorrhage	1938	Speer[27]
15.	62 years	M	R	410	Thrombus of coronary artery, recent infarct of myocardium	1947	Roberts and Loube[31] (case 1)
16.	65 years	M	R	—	Pneumonia	1931	Kintner[18]
17.	Adult	—	L	—	—	1898	Engleman[9]

* Left or right side.

† "persistence and detorsion of bulbus cordis, partial transposition of aorta, interauricular and interventricular septal defects, ductus arteriosus, sinistroposition of right auricle and right aortic arch."

‡ Saccular dilatation of aortic sinus from which missing coronary artery normally arises.

remaining normal vessel. This has been attributed to misplacement of the septum dividing the truncus communis into pulmonary artery and aorta with crowding together of the coronary artery anlagen.[31] The distribution of the single vessel in these cases is that of the normal right and left coronary arteries. These cases make up table 2. Sanes[33] stated that sinus at the site from which the missing vessel normally arises suggests that this represents a remnant of an absent coronary anlage and that the entire coronary arterial system in these cases arises from one coronary anlage. However, of the 8 cases in which such a saccular dilatation was present, the distribution of the single vessel in 2 cases was that of both the

normal right and left coronary arteries. Since the question of absence or misplacement of one coronary anlage may be considered unsettled, it is preferable at present to record cases of single coronary artery as such, rather than as cases of anomalous origin of one coronary artery or as cases of absent coronary artery.

There were 27 cases of single coronary artery occurring in adults. Of these, 18 were men and 8 were women. In one case the sex of the patient was not stated. The average age of the adult cases was 45 years and the oldest patient was 80. There were 13 cases of single right coronary artery and 15 cases of single left coronary artery. In 3 cases occurring in adults, the single artery was not named or described. In 7 cases in which the single vessel was present in the distribution of only one normal coronary artery, the average heart weight was 380 grams, with extremes of 150 and 520 grams, respectively. Similar data in the 7 cases in which the single vessel was present in the distribution of both coronary arteries revealed that the average heart weight was 505 grams, with extremes of 240 and 930 grams, respectively. Signs or symptoms of decreased cardiac function were not described in any case of single coronary artery in which autopsy examination revealed an otherwise normal cardiovascular system. In none of the cases of single coronary artery occurring in adults were other anomalies of the cardiovascular system reported.

Of the 27 adults with single coronary artery the cause of death was reported as related to cardiac disease in 9 cases. Autopsy examinations revealed a recent infarct of the myocardium in 3 cases and an old infarct in one case. The extent of the infarct was described in case 1 of the series of Roberts and Loube.[31] Here the right atrium and a large part of the

TABLE 3.—*Atypical Distribution of the Single Coronary Artery*

No.	Age	Sex	Single Artery Present*	Weight of Heart	Autopsy	Year	Author
				grams			
1.	Fetus, 6 months	M	—	—	Cor biloculare	1827	Mayer[3]
2.	Newborn	M	—	—	Cor biloculare	1847	Forster[5]
3.	Newborn	M	L	—	Bicuspid aortic valve	1890	Preisz[8] (case 1)
4.	2 days	F	—	—	Cor triloculare biatriatum	1848	Clark[6]
5.	3 days	F	R	—	Bronchopneumonia†	1947	Roberts and Loube[31] (case 8)
6.	4 days	M	L	—	Bicuspid aortic valve	1890	Preisz[8] (case 2)
7.	7 days	M	R	—	Hypoplasia of left ventricle and aorta†	1947	Roberts and Loube[31] (case 9)
8.	3 months	M	L	—	—	1924	Henke and Lubarsch[13]
9.	3 months	—	—	—	Bronchopneumonia	1931	Geever and Ravin[24]
10.	5 months	F	—	—	Cor biloculare	1931	Tow[28]
11.	6 months	F	L	—	Atresia pulmonic artery, absent tricuspid valve	1931	Kugel[21] (case 1)
12.	5 years	M	L	160	Stensosis pulmonic conus, persistent truncus communis	1918	deVries[11] (case 4)
13.	Young adult	M	L	370	Bicuspid aortic valve	1937	Richter[25] (case 2)
14.	22 years	M	L	—	—	1947	Roberts and Loube[31] (case 5)
15.	38 years	F	L	300	Thrombus of coronary artery, recent infarct of myocardium†	1947	Roberts and Loube[31] (case 3)

* Left or right side.

† Saccular dilatation of aortic sinus from which missing coronary artery normally arises.

right ventricle revealed a recent infarct. There was a recent thrombus of the first portion of a single right coronary artery. The diagnoses of the 9 cases in which cardiac disease was present are shown in table 4.

Single coronary artery was reported in 13 infants and one child. In 11 of these cases the distribution of the single vessel was atypical and did not resemble that of either the right or left coronary artery. In 9 of the 14 cases

TABLE 4.—*Cardiac Lesions Found in Cases of Single Coronary Artery*

Autopsy	Age	Author
1. Subacute bacterial endocarditis	37	Plaut[12]
2. Hemopericardium	37	Roberts and Loube[31] (case 6)
3. Thrombus of single coronary artery. Recent infarct of myocardium	38	Roberts and Loube[31] (case 3)
4. Rheumatic myocarditis	42	Maddox and Ibister[29]
5. Chronic endocarditis of mitral and aortic valves	45	Gallavardin and Ravault[14]
6. Thrombus of single coronary artery. Recent infarct of myocardium	46	Smith and Graber[15]
7. Old infarct of myocardium	46	Roberts and Loube[31] (case 4)
8. Chronic endocarditis of mitral and aortic valves	60	Bochdalek[7]
9. Thrombus of single coronary artery. Recent infarct of myocardium	62	Roberts and Loube[31] (case 1)

there were other anomalies of the cardiovascular system. These included cor biloculare, bicuspid aortic valve, cor triloculare biatriatum and hypoplasia of the aorta and left ventricle. Of these 14 cases of single coronary artery, one child lived to the age of 5 years, but of the remainder, the oldest lived to the age of 7 months.

SUMMARY

Forty-three cases of single coronary artery have been reported. This anomaly is thought to be due to absence or misplacement of one coronary artery anlage. In the absence of cardiovascular disease or other anomalies of the heart, single coronary artery is not associated with decreased cardiac function. Autopsy examination of an infant with a single coronary artery usually reveals other anomalies of the heart and great vessels and an atypical distribution of the single vessel. Two additional cases of single coronary artery are reported, one occurring in a white woman 80 years of age.

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Effect of Digitalis on the Clotting of the Blood in Normal Subjects and in Patients with Congestive Heart Failure

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Two groups of subjects were studied in order to evaluate the effect of digitalis on the coagulation of blood. One consisted of hospital patients in congestive heart failure, the other of normal interns. Control determinations were made of clotting and prothrombin times. Various preparations of digitalis were then administered in therapeutic doses. During administration, serial determinations were made of clotting and prothrombin times. The results were tabulated and the effect of digitalis appraised.

INTEREST in the intravascular clotting of the blood has been stimulated by the introduction into clinical usage of the anticoagulants, heparin and dicumarol. They have proved of particular value in the treatment in various disorders of the cardiovascular system in which thrombosis and embolism are so often disturbing complications. It is in this very group of diseases that digitalis is commonly employed as a therapeutic agent; and it has been claimed by various workers that this drug exerts an action in the body which favors coagulation of the blood. If true, it might be advisable to employ digitalis with caution, or perhaps avoid its use in those conditions in which it is most effective. In order to obtain further information on this point the present study was undertaken.

Tanaka[1] first drew attention to the thromboplastic action of the digitalis group of drugs, stating that strophanthin shortened the clotting time of the blood. Werch[2] described a 25 per cent decrease in the clotting time in rabbits following adequate digitalization. Decourt and Barbato[3] reported a decrease in blood coagulation time in 32 digitalized patients. Massie, Stillerman, Wright, and Minnich[4] determined clotting times before and after digitalization in 24 patients and found an average decrease of 3.3 minutes.

On the other hand, Ramsey, Pinschmidt, and Haag[5] found no change in the blood coagulation time of dogs following a single dose of digitalis.

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Sokoloff and Ferrer[6] found no significant change in the blood clotting time of 10 patients in congestive failure following the administration of digitalis.

In 1943, Macht[7] reported that cats previously heparinized were much less susceptible to toxic doses of digitalis than were untreated animals. In his opinion this may have been due to counteraction of a thromboplastic function of the digitalis glycosides. During the same year de Takats[8] described a heparin tolerance test and in subsequent work with Trump and Gilbert[9] found that digitalized animals were unusually insensitive to heparin administration. Moses,[10] using a similar test, found no decrease in the clotting time and no change in the response to heparin following the intravenous injection of digitalis.

Poindexter and Meyers[11] observed no alteration in the prothrombin times following adequate doses of digitalis.

Material

Two groups of subjects were studied before and after digitalization: (1) 17 cardiac patients in congestive heart failure; (2) 21 normal hospital interns and medical students. A third group of 14 hospital patients were used as controls. The latter were hospitalized for various reasons but none had liver disease or any disorder of the blood-forming organs. None received any medication which might affect blood clotting, nor was any given digitalis. Coagulation times were determined by two methods, the Lee-White and the Leifer, before digitalization and daily for a period of five days following digitalis therapy. Prothrombin times were determined at the same time on both undiluted plasma and plasma diluted eight times with normal salt solution (12.5 per cent plasma). Since the cardiac patients were all in moderate or severe congestive failure, it was

considered undesirable to make more than one observation before digitalis was given in order to avoid delay in carrying out treatment.

Of the patients in congestive failure, 14 were digitalized with the purified glycoside, digitoxin; these received 1.5 mg. to 2.4 mg. in five days. The average dose was 2.1 milligrams. The remaining 3 patients were digitalized with lanatoside C. Two of these received 1.6 mg. initially by intravenous injection and during the subsequent four days were given 1.2 mg. digitoxin by mouth. The third patient received 1.2 mg. lanatoside C intravenously and a total of 5 U.S.P. XII units of digitalis leaf by mouth during the next five days. In all patients the desired therapeutic response was obtained clinically.

Of the group of normal subjects who were digitalized, 4 received digitalis leaf. The total dosage for five days ranged from 18 to 20 U.S.P. XII units, the average dose being 19.8 units. The remaining 17 subjects received the glycoside, digitoxin. The total dosage for five days ranged from 1.8 mg. to 3.0 mg., the average dosage being 2.0 milligrams. In this group the clinical therapeutic effect of digitalis was, of course, not obtained. However, it should be noted that two of the subjects experienced minor toxic symptoms. One of these (H.A.) received 21 U.S.P. XII units of digitalis leaf and the other (R.C.) 3 mg. digitoxin. In the first patient anorexia and a few premature ventricular beats were noted. In the second a bigeminal pulse appeared and persisted for four days.

Methods

No subjects were included in the study who did not have easily accessible veins, and in all instances in which there was any difficulty with the venipuncture the specimen was discarded. Blood was removed with a 19-gage needle, the tourniquet being released as soon as the vein was entered.

Clotting Times. (A) Lee-White Method: The technic used was a slight modification of that described by Lee and White.[12] Three 75- by 10-mm. test tubes were placed in a warm water bath, the temperature of which was maintained between 36 and 39 Centigrade. One cubic centimeter of venous blood was placed carefully into each of the tubes. At the end of three minutes the first tube was tilted to the horizontal. This procedure was repeated every thirty seconds until the blood was seen to clot. The second tube was then similarly tilted and finally the third. The clotting time was considered to be the number of minutes which had passed when the blood in the third tube failed to flow down the side. To time the experiment the stop watch was arbitrarily started when one-half the total volume of the desired blood had been drawn into the syringe. All test tubes were cleansed daily with soap and water, potassium dichromate and concentrated sulfuric acid, and were rinsed with distilled water and oven-dried.

(B) Leifer Method[13]: Ten 75- by 10-mm. test tubes were placed in a warm water bath with the temperature maintained between 36 and 39 C. To each of these tubes was gently added 0.5 cc. of the subject's blood. The stopwatch was started as described above. At the end of the third minute the first tube was removed from the water bath, corked, rapidly inverted, and placed in a test tube rack while still inverted. At the end of each successive minute another tube was similarly inverted until all ten tubes had been removed from the bath. The end point was considered to be the time represented by that tube in which there first appeared a definite film of clot which remained at the bottom of the tube following inversion.

Prothrombin Times. These were determined by a slight modification of the Link-Shapiro adaptation of Quick's method.[14] The times are expressed in seconds. Into a chemically clean and oven-dried test tube was placed 0.01 gram potassium oxalate. To this were added 5.0 cc. of the subject's blood. The oxalated blood was centrifuged, and the plasma decanted and placed in a water bath maintained at 36 to 39 C. Fifty milligrams of desiccated rabbit lung* were diluted with 2.5 cc. of normal saline. This mixture was stirred vigorously for ten minutes in a water bath at 54 to 58 C. It was then cooled to 25 C. and 2.5 cc. of 0.025 molar calcium chloride were added. The resulting mixture was stirred for four minutes, centrifuged, and the supernatant fluid decanted. Two-tenths cubic centimeter of this solution was then placed in a 75- by 10-mm. test tube in a warm water bath (36 to 39 C.). When the calcium chloride-thromboplastin mixture had reached the temperature of the bath, 0.1 cc. of plasma was added. The mixture was vigorously stirred with a wire loop. The time was

* Prepared by the Maltine Company, New York, N. Y.

measured from the moment the first drop of plasma came into contact with the calcium chloride-thromboplastin mixture until a firm clot formed across the loop.

An identical procedure was carried out on both undiluted and 12.5 per cent plasma. In the latter case a normal solution of saline was used to dilute the plasma 1 to 8. A normal control blood was drawn each day within one hour of the time blood was obtained from the subject studied. Duplicate determinations were performed on each sample of the subject and the control blood throughout the study. Each prothrombin time listed in the tables represents the average of two determinations.

Results

Clotting Times. Using the Lee-White method, the average coagulation time of normal controls, including both the group of 13 undigitalized hospital patients and the group of 21 normal interns, before digitalization was 11.6 minutes. The overall range included the extremes of 8.5 minutes and 19.0 minutes. With the Leifer method the average time for the same group was 6.2 minutes with a range of 4 to 10 minutes. There was found to be a considerable degree of variation of coagulation times between individuals. However, individual subjects remained fairly constant throughout the study. Frequent determinations revealed that those subjects with somewhat longer clotting times tended to retain them from day to day. The same was true of those subjects with the shorter times.

In the group of patients in congestive failure the average coagulation time before digitalization was 11.9 minutes by the Lee-White method. Following digitalis the average time was 11.1 minutes, the average change being −0.8 minutes or −7 per cent. By the Leifer method the average clotting times before and after digitalization were 6.1 minutes and 6.0 minutes respectively, with an average change of −0.1 minutes or −2 per cent.

In the group of normal subjects who were digitalized, the average coagulation times with the Lee-White method were 12.1 minutes before and 12.3 minutes following digitalization, with an average change of +0.2 minutes or +2 per cent. The average time with the Leifer method was found to be the same before and after digitalization, namely 6.6 minutes.

In the patients in the control group, who received no digitalis, the average time by the Lee-White method was 10.7 minutes at the start and 11.0 minutes at the end of the study, a change of +0.3 minutes or +3 per cent. With the Leifer method the corresponding times were 5.6 minutes and 6.3 minutes respectively; the change was +0.7 minutes or +13 per cent.

From the data in tables 1, 2, and 3, it will be noted that some individuals showed slight shortening of the clotting times while others showed prolongation. It will be further noted that the changes in the clotting times were not always in the same direction by the two methods used. There was no significant difference in the response of the coagulation time to digitalis between patients in congestive failure and normal individuals. The degree of change noted in these two groups was of no greater magnitude than that noted in members of the control group who received no digitalis. Although considerable variation was found in clotting times when comparing individuals, the average times in all groups were of a similar degree of magnitude, and the average change following digitalization was small and statistically insignificant. There was very little change in the daily averages of the clotting times throughout the study.

Prothrombin Times. Using undiluted plasma the average prothrombin times of normal controls, including both the members of the group of undigitalized hospital patients and those of the group of normal interns, before digitalization was 13.34 seconds. The extremes were 11.9 seconds and 17.8 seconds. All but one determination on one subject fell within the range of 13.5 seconds ±1.6 seconds.

In the case of 12.5 per cent plasma the average prothrombin time of the same group of normals was 31.0 seconds with an over-all range of 25.5 seconds to 42.5 seconds. With the diluted plasma the range was found to be quite wide and the end point less reliable.

In the group with congestive failure the average times in seconds, using 100 per cent plasma, were 14.6 before and 13.8 after digitalization,

TABLE 1.—*Patients in Congestive Heart Failure before and after Digitalization*

Patient No.	Age (years)	Diagnosis	Total Digitalis in Five Days	Clotting Time of Blood (Minutes)						Prothrombin Time of Plasma (Seconds)					
				Lee-White Method			Leifer Method			Undiluted Plasma			2.15% Plasma		
				Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change
1	56	Coronary sclerosis	1.7 mg. digitoxin	8.5	10.0	+1.5	4.0	5.0	+1.0	13.1	11.2	−1.9	28.1	26.8	−1.3
2	82	Hypertensive cardiovascular disease	2.2 mg. digitoxin	10.0	9.0	−1.0	5.0	6.0	+1.0	13.2	14.1	+0.9	35.0	47.0	+12.0
3	56	Hypertensive cardiovascular disease	1.6 mg. lanatoside C 1.2 mg. digitoxin	8.5	8.0	−0.5	4.0	5.0	+1.0	13.7	13.6	−0.1	32.8	21.8	−11.0
4	52	Myocardial infarction	1.8 mg. digitoxin	8.5	10.0	+1.5	5.0	4.0	−1.0	13.4	13.0	−0.4	33.3	25.2	−8.1
5	65	Coronary sclerosis	1.5 mg. digitoxin	9.5	11.5	+2.0	5.0	5.0	0.0	13.8	13.2	−0.6	33.3	33.1	− 0.2
6	65	Cor pulmonale	2.3 mg. digitoxin	9.0	8.5	−0.5	5.0	5.0	0.0	15.7	13.1	−2.6	27.0	25.3	−1.7
7	64	Cor pulmonale	2.4 mg. digitoxin	15.0	9.0	−6.0	9.0	6.0	−3.0	17.9	14.4	−3.5	55.5	32.2	−23.3
8	56	Coronary sclerosis	1.2 mg. lanatoside C 4 U digitalis	13.5	13.5	0.0	8.0	9.0	+1.0	14.6	20.0	+5.4	32.4	34.6	+2.2
9	20	Cor pulmonale	1.8 mg. digitoxin	9.5	8.5	−1.0	4.0	4.0	0.0	15.3	14.0	−1.3	32.1	33.3	+1.2
10	73	Coronary sclerosis	2.4 mg. digitoxin	10.0	10.0	0.0	5.0	5.0	0.0	13.9	12.2	−1.7	27.8	24.2	−3.6
11	46	Thyrotoxicosis	1.6 mg. digitoxin	11.5	11.5	0.0	6.0	5.0	−1.0	12.3	14.5	+2.2	35.8	33.4	−2.4
12	67	Hypertensive cardiovascular disease	2.2 mg. digitoxin	14.0	14.0	0.0	5.0	6.0	+1.0	13.5	13.9	+0.4	27.7	30.8	+3.1
13	52	Myocardial infarction	2.4 mg. digitoxin	11.0	14.0	+3.0	8.0	7.0	−1.0	16.4	13.6	−2.8	36.9	34.9	−2.0
14	43	Hypertensive cardiovascular disease	1.6 mg. lanatoside C 1.2 mg. digitoxin	16.0	13.0	−3.0	9.0	8.0	−1.0	14.0	12.7	−1.3	26.1	24.3	−1.8
15	49	Myocardial infarction	2.4 mg. digitoxin	20.5	19.5	−1.0	10.0	11.0	+1.0	14.5	13.8	−0.7	27.5	26.1	−1.4
16	51	Rheumatic heart disease	2.4 mg. digitoxin	10.5	9.5	−1.0	5.0	5.0	0.0	20.5	13.5	−7.0	35.0	35.1	+0.1
17	66	Myocardial infarction	1.7 mg. digitoxin	16.0	8.5	−7.5	6.0	6.0	0.0	12.6	14.4	+1.8	23.2	22.7	−0.5

TABLE 2.—*Normal Subjects before and after Digitalization*

Subject No.	Age (years)	Total Digitalis	Clotting Time of Blood (Minutes)						Prothrombin Time of Plasma (Seconds)					
			Lee-White Method			Leifer Method			Undiluted Plasma			12.5% Plasma		
			Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change
1	25	20 U. digitalis	16.25	15.0	−1.25	9.5	9.0	−0.5	12.0	12.9	+0.9	28.1	31.8	+3.7
2	25	18 U. digitalis	18.5	14.5	−4.0	9.0	10.0	+1.0	13.1	13.2	+0.1	32.1	34.2	+2.1
3	25	20 U. digitalis	14.5	16.5	+2.0	10.0	9.0	−1.0	13.0	14.9	+1.9	25.9	31.7	+5.8
4	24	21 U. digitalis	17.5	15.0	−2.5	9.0	9.0	0.0	12.8	13.1	+0.3	27.6	32.7	+5.1
5	24	2.0 mg. digitoxin	12.75	8.5	−4.25	6.5	5.0	−1.5	12.2	13.6	+1.4	29.8	31.0	+0.2
6	22	2.0 mg. digitoxin	8.5	9.0	+0.5	5.0	5.0	0.0	15.0	14.9	−0.1	42.5	36.3	−6.2
7	22	2.0 mg. digitoxin	9.0	8.0	−1.0	4.0	4.0	0.0	11.9	12.9	+1	31.3	28.6	−2.7
8	22	2.0 mg. digitoxin	8.5	8.5	0.0	5.0	4.0	−1.0	12.9	17.1	+4.2	37.1	39.9	+2.8
9	21	2.0 mg. digitoxin	9.0	9.0	0.0	5.0	5.0	0.0	13.2	15.1	+1.9	30.7	27.9	−2.8
10	22	1.8 mg. digitoxin	10.0	9.0	−1.0	5.0	5.0	0.0	13.4	15.0	+1.6	37.5	34.4	−3.1
11	22	2.0 mg. digitoxin	9.0	9.0	0.0	6.0	6.0	0.0	13.3	13.6	+0.3	34.5	32.9	−1.6
12	22	2.2 mg. digitoxin	8.75	9.0	+0.25	5.0	5.0	0.0	12.3	12.2	−0.1	32.9	33.1	+0.2
13	24	1.8 mg. digitoxin	19.0	18.0	−1.0	9.5	9.0	−0.5	14.6	14.1	−0.5	30.7	33.0	+2.3
14	24	2.0 mg. digitoxin	16.5	17.0	+0.5	7.0	9.0	+2.0	13.1	13.0	−0.1	28.8	30.0	+1.2
15	24	2.0 mg. digitoxin	14.5	17.5	+3.0	7.0	7.0	0.0	13.0	13.0	0	31.8	33.2	+1.4
16	24	1.8 mg. digitoxin	17.75	14.5	−3.25	8.5	10.0	+1.5	13.2	10.4	−2.8	31.5	28.1	−3.4
17	24	2.0 mg. digitoxin	17.5	14.5	−3.0	8.0	6.0	−2.0	11.9	11.9	0	32.9	33.2	+0.3
18	24	1.8 mg. digitoxin	10.0	10.0	0.0	5.0	5.0	0.0	14.2	12.3	−1.9	31.8	34.7	+2.9
19	24	1.8 mg. digitoxin	9.0	10.0	+1.0	5.0	5.0	0.0	13.8	13.2	−0.6	37.3	34.3	−3.0
20	24	1.8 mg. digitoxin	10.0	9.0	−1.0	5.0	6.0	+1.0	13.5	13.1	−0.4	33.6	31.7	−1.9
21	32	3.0 mg. digitoxin	9.0	16.0	+7.0	5.0	7.0	+2.0	12.5	13.7	+1.2	33.2	32.4	−0.8

TABLE 3.—*Normal Controls—Undigitalized*

Control No.	Age (years)	Diagnosis	Clotting Time of Blood (Minutes)						Prothrombin Time of Plasma (Seconds)					
			Lee-White Method			Leifer Method			Undiluted Plasma			12.5% Plasma		
			Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change	Initial	Final	Net Change
1	27	Normal	11.5	9.0	−2.5	5.0	5.0	0	12.4	12.6	+0.2	27.3	30.3	+3.0
2	70	Marginal gastric ulcer	11.0	9.5	−1.5	5.0	5.0	0	13.2	14.5	+1.13	27.2	26.4	−0.8
3	35	Epilepsy; anxiety state	13.5	11.5	−2.0	5.0	8.0	+3.0	13.9	12.2	−1.7	29.8	25.8	−4.0
4	21	Pericarditis	12.0	14.5	+2.5	6.0	8.0	+2.0	14.5	13.4	−1.1	30.4	28.7	−1.7
5	47	Gastric ulcer	8.5	10.0	+1.5	6.0	5.0	−1.0	12.4	13.6	+1.2	30.0	29.0	−1.0
6	45	Malaria	9.0	14.0	+5.0	7.0	7.0	0	13.0	14.4	+1.4	27.0	26.5	−0.5
7	53	Myocardial infarction	9.5	10.0	+0.5	5.5	5.0	−0.5	17.8	13.7	−4.1	28.0	32.8	+4.8
8	49	Lobar pneumonia	11.5	9.5	−2.0	6.0	5.0	−1.0	13.5	13.7	+0.2	27.3	27.8	+0.5
9	65	Coronary sclerosis	11.5	12.0	+0.5	7.0	8.0	+1.0	15.0	13.7	−1.3	25.5	32.8	+7.3
10	42	Duodenal ulcer	9.5	9.5	0.0	5.0	5.0	0	11.9	12.3	+0.4	28.8	32.6	+3.8
11	78	Coronary heart disease	11.0	13.0	+2.0	5.0	7.0	+2.0	13.3	15.0	+1.7	26.4	34.2	+7.8
12	13	Acute glomerulonephritis	11.5	11.5	0	5.0	8.0	+3.0	13.4	12.9	−0.5	35.5	39.6	+4.1
13	32	Normal	9.5	9.0	−0.5	6.0	5.0	−1.0	13.3	12.5	−0.8	33.0	33.2	+0.2

a change of −0.8 seconds or −5 per cent. In the same group of patients with 12.5 per cent plasma the average times before and after digitalization were 32.3 seconds and 30.0 seconds respectively, a change of −2.3 seconds or −7 per cent.

In the group of normal subjects who were digitalized the average initial time with 100 per cent plasma was 13.1 seconds, the average final time 13.5 seconds, a change of +0.4 seconds or +3 per cent.

In the control group the average initial time with undiluted plasma was 13.6 seconds, the final time 13.4 seconds, a change of −0.2 seconds or −2 per cent. With 12.5 per cent plasma the average times were 28.9 seconds and 30.7 seconds, an average change of +1.8 seconds or +6 per cent.

As in the case of the coagulation times, there appeared to be no constant trend toward either a prolongation or a shortening of the prothrombin time. The average time at the start of the study was comparable in all groups and the daily average changes following digitalization were small and of no greater degree than those noted in patients who received no digitalis. Essentially the same results were noted using both diluted and undiluted plasma.

None of the differences observed, either in clotting or prothrombin times, were statistically significant.

Conclusions

The action of digitalis on the clotting time and prothrombin time was investigated in 17 cardiac patients in congestive heart failure and in 21 normal subjects to determine the effect of this drug, in therapeutic doses, on the clotting function of the blood.

There were no statistically significant changes in either clotting or prothrombin times following the administration of digitalis.

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The Rate of Disappearance of Lanatoside C. and Digitoxin from the Blood of Rats

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With the technical assistance of Catherine Bland, A.B.

By means of the embryonic duck heart preparation, both lanatoside C. and digitoxin could be detected and quantitatively measured in the sera of rats after parenteral administration of both drugs. A study of the behavior of the two glycosides in blood indicated that a striking difference existed in the respective rates of disappearance of both drugs from the bloodstream.

THE RAPID disappearance of lanatoside C. from the blood stream of human subjects who had received 1.2 mg. of the drug by intravenous injection already has been reported by us.[1] It also was thought desirable to determine the rate of disappearance of the same drug and of digitoxin from the blood of rats after the latter had received either of the two drugs by intravenous injection. The results of such a study are herein reported.

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Methods

Normal male, adult, albino rats (average wt.: 125 grams) were employed in the study. One series of rats (73) was given lanatoside C., 1.0 μg per Gm. of body weight, by vein. Single blood samples (2.0 to 3.0 cc.) then were obtained from these rats 1, 3, 5, 10, 15, 20, 30, and 60 minutes after the introduction of the drug. Each sample was allowed to clot, then centrifuged, the serum removed and stored in the refrigerator for twenty-four hours. The serum samples then were assayed for their lanatoside C. content by the employment of embryonic duck hearts, as previously described.[2]

Another comparable series of rats (179) was given digitoxin (Sandoz), 1.0 μg per Gm. of body weight, by vein. Blood samples were obtained 5, 20, 30, and 60 minutes; also at 2, 4, 6, 8, 12, 16, and 24 hours after injection. These were treated and assayed exactly as described above.

Table 1.—*The Rate of Disappearance of Lanatoside C. and Digitoxin from Serum of the Rat*

Time After Inj.	No. Rats	Lanatoside C. (serum) (μg/cc)		No. Rats	Digitoxin (serum) (μg/cc.)	
		Average	Range		Average	Range
1 min.	4	5.2	5.0 to 5.5			
3 min.	3	3.7	2.0 to 6.0			
5 min.	8	0.48	.40 to 7.0	10	2.1	1.2 to 2.7
10 min.	11	0.27	.15 to 0.40			
15 min.	14	0.20	.15 to 0.30			
20 min.	13	0.18	.15 to 0.30	10	1.8	1.4 to 2.0
30 min.	15	0.13	.05 to 0.20	17	1.5	1.2 to 1.8
60 min.	5	N.D.*	N.D.	19	1.0	0.5 to 1.6
2 hrs.	—	—	—	14	0.9	.7 to 1.60
4 hrs.	—	—	—	17	0.6	.4 to 0.80
6 hrs.	—	—	—	26	0.38	.15 to 0.65
8 hrs.	—	—	—	21	0.33	.1 to 0.6
12 hrs.	—	—	—	12	0.25	N.D. to 0.6
16 hrs.	—	—	—	19	0.13	N.D. to 0.4
24 hrs.	—	—	—	14	N.D.	N.D.

* N. D. = No glycoside detected.

Results

Rate of Disappearance of Lanatoside C. Lanatoside C. was found (see table 1) to disappear very quickly from the serum of the injected rats. Although each cc. of serum contained 5.2 μg one minute after injection, only 0.48 μg could be found five minutes after injection. No lanatoside C. (i.e., less than 0.05 μg per cc. of serum) could be detected in the serum of any of five rats an hour after the intravenous injection of the drug.

Rate of Disappearance of Digitoxin. The intravenous injection of digitoxin into the rats could not be done quickly because of the large amount of alcohol (in which the digitoxin was dissolved) which also had to be injected. The first blood samples, therefore, were obtained approximately five minutes after the beginning of the injection. As table 1 indicates, digitoxin, unlike lanatoside C., disappeared from the blood stream at a relatively slow rate. Thus, its average concentration at the end of five minutes was 2.1 μg per cc. of serum. The concentration then slowly dropped until, at the end of an hour, only 1 μg per cc. remained. Although there was little decrease during the second hour, a progressive diminution occurred after that up to the sixth hour, after which time the concentration of digitoxin remained relatively constant until the eighth hour. After the eighth hour, it progressively decreased so that, whereas small amounts of digitoxin could be detected in the serum of most of the rats sixteen hours after injection, none was found twenty-four hours after injection.

Discussion

In the above experiments, sufficient cardiac glycosides were administered (1 μg per gram of body weight) so that if complete diffusion of the drugs occurred throughout the tissues of the rat, each gram of tissue, including the blood, should contain 1 μg of glycoside. However, within thirty minutes after its intravenous injection, the concentration of lanatoside C. in serum fell to 0.13 μg per cc. Within an hour, moreover, none could be detected. This experimental finding not only indicated that lanatoside C. left the blood stream extraordinarily rapidly, but also that some tissue (or tissues) other than blood was (1) excreting, (2) destroying, or (3) storing the glycoside.

On the other hand, digitoxin did not appear to leave the blood stream at nearly so rapid a rate. The probable adsorption of this drug by the plasma proteins[3] perhaps accounts for its persistence in the blood for over twelve hours. However, its concentration in serum began to fall below 1 μg per cc. one hour after its injection, indicating that it, too, was being excreted, destroyed, or stored by some extravascular tissue(s).

Although no evidence was obtained in this present study concerning the exact cause of disappearance of the two glycosides from blood, it seems quite unlikely that a significant amount of digitoxin was excreted via the kidney because it was found in a previous study[4] that little or no digitoxin was excreted in the urine of rats receiving the amount of glycoside employed in the present study.

Conclusions

1. The rates of disappearance of both lanatoside C. and digitoxin from the blood of injected rats were studied.

2. Lanatoside C. disappeared from the blood of rats thirty to sixty minutes after the injection of 1 μg. per gram of body weight.

3. Digitoxin at the same dosage disappeared much more slowly from the blood.

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The Q-T Interval in the Electrocardiogram of Children with Tuberculosis

By THEODORE T. FOX, M.D., HERBERT BERGER, M.D., ELLIOTT KAPLAN, M.D., AND JOHN C. MARSHAL, M.D.

It is stated that prolongation of the Q-T interval is a reliable criterion of active carditis. A control investigation of a group of tuberculous children was undertaken with particular reference to this point. It was observed that prolongation of the Q-T interval is a rather frequent finding in childhood tuberculosis, but is not an expression of the cardiac status of the patient. The value of the Q-T interval as an indicator of active carditis is therefore questioned.

IT IS A well known fact that many cases of active rheumatic heart disease do not show the known criteria for "activity," namely, elevated temperature, elevated sedimentation rate, anemia, rapid ventricular rate, or fluctuating electrocardiographic findings. Every effort to establish objective criteria to include all cases of rheumatic activity is justifiable. Extreme caution, however, should be exercised in the selection of these criteria, so that persons without rheumatic activity are not branded with the mark of disability. The recent awakening of interest in the value of the Q-T interval in patients with acute carditis commands a series of control studies. If prolongation of the electrical systole is shown to occur non-specifically, then one can hardly be justified in dignifying this phenomenon with the quality of a selective criterion.

For the purpose of checking the significance of the Q-T interval in cases of carditis a group of 59 children in the age group of 7 to 14 years was studied electrocardiographically and the findings correlated with the clinical status of each patient. None had clinical or x-ray evidence of heart disease with the exception of one child who, in addition to pulmonary tuberculosis, had rheumatic heart disease. All of the children had tuberculosis; some had active and some, inactive lesions. A number of the children with inactive cases had upper respiratory infections at the time the tracings were recorded. This was thought to account for the transient rise in temperature or sedimentation rate.

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As the age group of the patients selected for the study was the same as that of the patients reported in the paper by Taran and Szilagyi,[1] the same method of measuring the Q-T interval in the electrocardiogram was adopted in order to make our results comparable to theirs. In patients with sinus arrhythmia a sequence of several beats was averaged in the calculation of the Q-T time. At all times an average of the Q-T interval in the various leads was taken, although actually the longest Q-T interval in any of the leads is the correct one.

The Q-T, corrected in relation to the heart rate, was calculated according to Bazette's formula: $QT_c = \frac{QT}{\sqrt{RR}}$, where Q-T is the Q-T interval in seconds, and RR is the cardiac cycle in seconds.[2] At the suggestion of Dr. Walter Modell,[3] the calculations were made with a slide rule as illustrated in figure 1. The measured Q-T is found on scale D. The slide is then moved to the point indicating the RR interval on scale B. The QTc is read on scale D, where the index I on C is in opposition with D. This calculation is rendered even more simple by the nomogram recently devised by Kissin, Schwarzschild, and Bakst.[4] Difficulties were encountered in measuring the Q-T interval in some cases. The high T waves present a well-defined end point, but the low, diphasic or inverted T waves have an end point not easily distinguishable. It appeared generally that

complexes with a high T wave had large Q-T intervals, and it thus naturally suggests itself that the length of the Q-T interval in complexes with low-amplitude T waves may not be the correct one, as a portion of this interval may be submerged in the isoelectric phase. In such cases the complexes with the clearly discernible end points were considered. The measurements were made with the aid of adequate illumination, a strong magnifying glass, and a pair of draftman's steel calipers. The readings were made against the time lines in the very sections where the graph was measured.

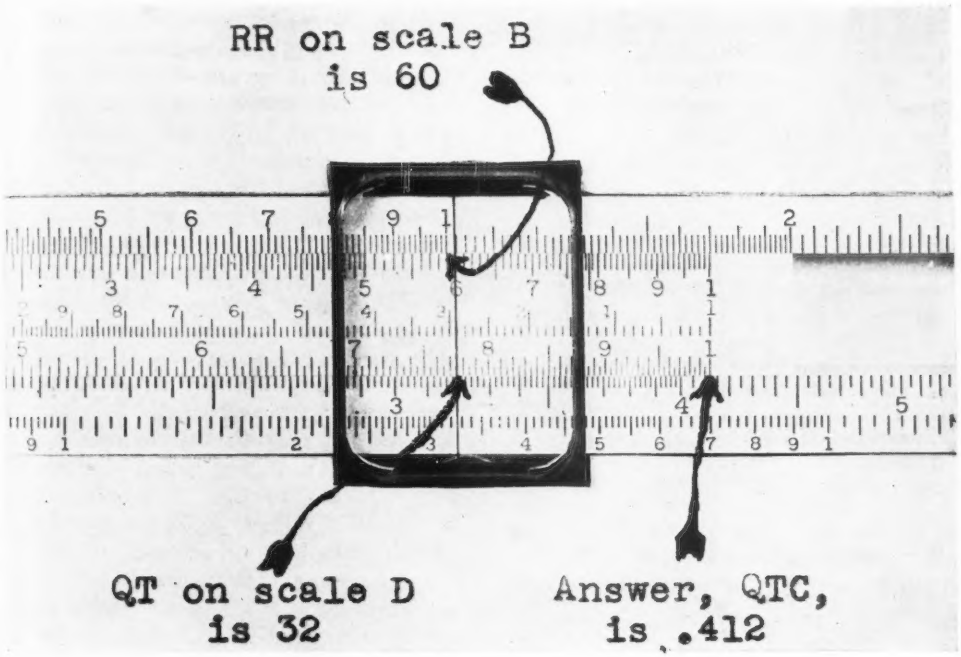

FIG. 1.—The slide-rule and the method of calculation of QT-c. (See text.)

RESULTS

Of the 59 children studied, 24 had active tuberculosis: 14 children had pulmonary disease and 10 had extrapulmonary lesions. In this "active" group, Q-T intervals longer that 0.405 seconds, considered by Taran and Szilagyi[1] as upper limit of normal, were observed in 7 children (29 per cent). Four children were in the pulmonary and 3 in the extrapulmonary group. The abnormal readings were as follows: 0.408, 0.415, 0.427, 0.426, 0.406, 0.408, 0.406.

In the "inactive" group there were 35 cases. Of these, 12 children had abnormal Q-T intervals (34 per cent). The readings were as follows: 0.419, 0.410, 0.455, 0.405, 0.460, 0.409, 0.417, 0.430, 0.411, 0.419, 0.410, 0.428.

In the "active" group there was one child with associated rheumatic fever; the Q-T interval in this child was only 0.4.

In the "inactive" group there was one child with a prolonged P-R interval but no confirming evidences of rheumatic fever. The Q-T interval in this child was 0.428.

The relationship of the QTc to temperature and sedimentation rate is indicated in table 1. It appears that in the group with abnormal QTc's, there was a predominance of patients with elevated sedimentation rates and elevated temperatures. However, the fact that in the group with normal QTc's the number of patients with elevated sedimentation rates with

or without elevated temperatures is about equal to the number of patients with normal temperatures and sedimentation rates, suggests the conclusion that temperature and the sedimentation rate are not important factors in determining the value of the Q-T interval. In 6 cases, records were secured under varying clinical circumstances. In 3 of these, previously normal QTc's became abnormal with a rise in sedimentation rate and/or temperature. In 2 cases, normal QTc's remained normal after sedimentation rate became elevated. In one case a normal QTc diminished in duration with a rise in the sedimentation rate.

As noted in table 1, 26 patients had normal temperatures and normal sedimentation rates at the time the tracings were secured; in 11 children, intercurrent upper respiratory infections were thought to be responsible for the

TABLE 1.—*Relationship of QTc to Temperature and Sedimentation Rate*

	Normal QTc	Abnormal QTc
Normal temp. and sed. rate.....	19	7
Normal temp. and elev. sed. rate...	13	7
Elev. temp. and elev. sed. rate.....	7	5
Elev. temp. and norm. sed. rate.....	0	1

slightly elevated temperature and equally slightly elevated sedimentation rate. One child had measles, and one had coexistent rheumatic heart disease.

As to the prognostic significance of the abnormally prolonged Q-T interval, the following is to be noted. Our study began in November 1947 and continued until the end of February 1948. By November 15, 1948, all children but one with prolonged Q-T intervals were discharged from the hospital in good condition ("arrested"). One was transferred to another institution while still showing activity of the primary complex.

COMMENT

If prolongation of the Q-T interval is an indication of myocardial disease, then 29 per cent of our patients with "active" cases and 34 per of those with "inactive" cases had myocarditis—presumably tuberculous in origin, or, differently stated, 35 per cent of the total group (20 out of 59) were afflicted with tuberculous myocarditis. This is quite an exaggerated figure in the light of the evidence in the literature on the subject. Admittedly, tuberculous myocarditis is much more commonly observed in children than in adults, but even in children the incidence is only about 3.9 percent.[5] The type of involvement reported in children has been chiefly that of miliary tubercles in the myocardium, probably attributable to the fact that in the great majority there was present generalized miliary tuberculosis.[5] Since none of the children studied have evidence of miliary tuberculosis, on clinical grounds at least the suspicion that some of the children had tuberculous myocarditis would hardly be justified. None of the tracings presented other than Q-T abnormalities to suggest myocardial damage; no conduction difficulties were seen in any but one child to suggest nodular infiltration of the myocardium. In a previous publication it was shown that a prolonged P-R interval in patients with pulmonary tuberculosis does not necessarily indicate myocardial damage.[6] The interstitial myocarditis observed in tuberculosis is ascribed to nontuberculous pulmonary infection by Roberts and Lisa.[7] None of our patients had clinical evidences of the associated pathologic process described by these authors.

It thus appears fairly certain that the Q-T abnormalities observed in our group are not expressions of tuberculous myocarditis. Just what is its significance is at present not known. Perhaps it is a function of a *nonspecific extracardiac* factor which participates in disease in general, an expression of disturbed biochemistry which is known to influence this particular segment of the electrocardiogram.[8–11]

The nondependence of the Q-T interval on the height of the sedimentation rate or temperature has already been commented on.

Could the Q-T interval be a sensitive indicator in rheumatic heart disease specifically and not any other type of carditis? The electrocardiogram was never thought to possess such *selective* properties.

Summary and Conclusion

Fifty-nine cases of pulmonary and extrapulmonary tuberculosis in children were studied with particular reference to the Q-T interval in the electrocardiogram. Thirty-five per cent of the patients of this group presented prolongation of the Q-T interval with no corroborative evidence of myocardial involvement. The frequency of the prolonged Q-T interval was greater in the group of patients with inactive tuberculosis than in the patients showing evidences of tubercular activity.

Doubt is expressed as to the diagnostic or prognostic significance of the prolonged Q-T interval. It is apparent from this study that in evaluating the myocardial state in tuberculosis the Q-T segment of the electrocardiogram does not contribute a reliable criterion. Furthermore, our observations apparently are not in accord with the idea that prolongation of the electrical systole is a specific finding in children with active rheumatic heart disease.

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Coronary Arteriography in the Intact Dog

By Felix Pearl, M.D., Meyer Friedman, M.D., Norman Gray, M.D., and Bruce Friedman, M.D.

A method is described whereby the coronary arteries of dogs with intact chests can be regularly demonstrated roentgenologically by the use of small amounts of Diodrast injected through a specially devised catheter which is passed to the aortic sinus through a peripheral artery. The artery is preserved by suture. Electrocardiograms taken during the procedure were normal. The aortic valves of two excised hearts previously subjected to forceful trauma by the catheter, showed no abnormality. Characteristic arteriograms are reproduced, showing coronary arteries, separate cusps of the aortic valves, and the proximal aorta.

UNTIL RECENTLY, no satisfactory method has been available for the safe and dependable roentgenologic visualization of the proximal aorta and the aortic arch. In an attempt to produce such a method, one of us (F. P.)[3, 4] has devised and reported a special thin-walled, woven nylon, radio-opaque catheter* which may be inserted into a peripheral artery and easily passed to the proximal aorta or the left ventricle under fluoroscopic control. The catheter is so constructed that by manual syringe pressure alone it can deliver 5 cc. per second of radio-opaque liquid against the force of the arterial pressure. The outside diameter of the catheter is small enough so that the artery of insertion can be preserved by suture when the catheter is withdrawn. Details of the use of the catheter will be reported in subsequent communications.

This method of precision retrograde aortography was utilized in an attempt to demonstrate the coronary arteries of the intact dog. The catheter was passed to the aortic sinus (of Valsalva) through an opening in the carotid or the femoral artery. For the precise placement of the catheter and the actual arteriography, the animal was placed on its left or right side. The heart when x-rayed from the lateral position was clearly seen without the interference of the shadows cast by the vertebral column. Many experiments were conducted, altering the position of the catheter or the temporal relationship between injection of radio-opaque medium and x-ray exposure. Finally, we were successful in obtaining consistently clear-cut, contrasting coronary arteriograms with an injection of only 4 cc. of 70% Diodrast† solution, of which at least 1.5 cc. was used in filling the catheter itself (figs. 1, 2, and 3). Electrocardiograms taken during the time the catheter was in place, and during and after the injection of Diodrast, showed no abnormality.

The catheter was connected to a special pressure apparatus which kept its lumen clear with a small steady stream of heparinized normal salt solution. It was then inserted into the exposed and stripped peripheral artery so that there was no leakage, and passed proximal. The angulated tip allowed it to follow the curve of the aortic arch and to approach the heart. Precise placement of the catheter was then done under fluoroscopic control. When the catheter contacted the aortic valves, a characteristic sense of resistance was communicated to the hand of the operator; one observed also in the fluoroscope that the catheter buckled slightly and the whipping motion of the tip was restricted. The forward pressure on the catheter then was released and it was withdrawn under fluoroscopy about 0.5 cm. until the operator was certain that the tip of the catheter lay free and mobile in the main aortic current. Blood was aspirated from and injected gently through the catheter in order to make sure that the

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* The catheters were generously furnished by Mr. Norman Jaeckel, president of the U. S. Catheter and Instrument Co., Glens Falls, N. Y.

† The Diodrast was generously supplied by Winthrop-Stearns, Inc., New York, N. Y.

openings in the catheter were not blocked by impingement against the aortic valves or wall. The x-ray apparatus was arranged for $\frac{1}{20}$ second Bucky exposure. The pressure apparatus containing salt solution was disconnected and replaced by a Robb syringe containing 4 cc. of 70 per cent Diodrast. Blood was prevented from regurgitating through the catheter by steady manual pressure upon the plunger. The operator then injected the solution as quickly as possible, beginning $\frac{1}{3}$ to $\frac{1}{2}$ second before the first roentgen exposure. Using a tunnel, two exposures were taken about $\frac{1}{10}$ to $\frac{1}{5}$ second apart. The syringe was replaced by the pressure apparatus and the films were developed. If necessary, additional films were taken, using variations of the technique indicated by the ones already exposed.

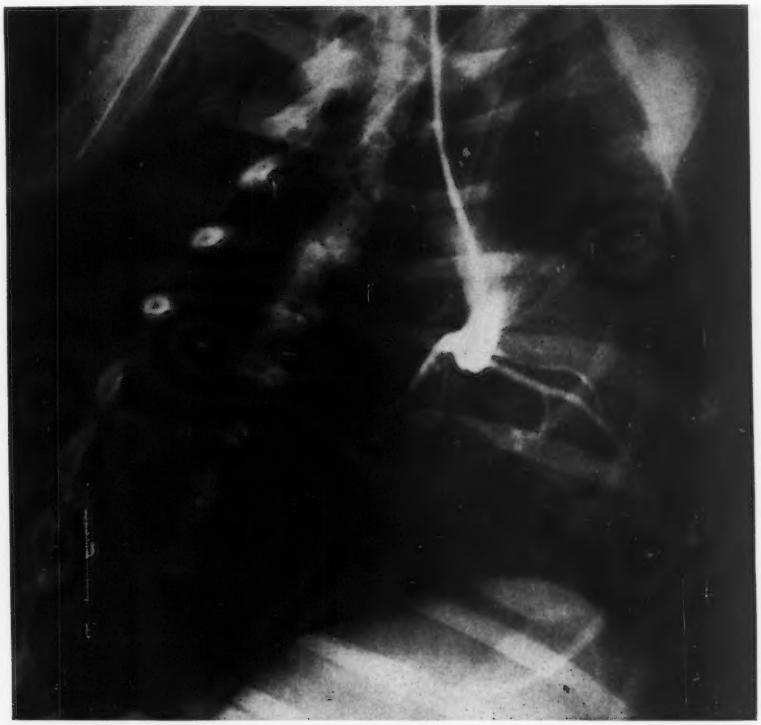

FIG. 1.—Dog. Intact chest. Right side down. Special arterial catheter inserted to aortic sinus through the carotid artery. Only 4 cc. of 70 per cent Diodrast injected. The right, left anterior descending and left circumflex arteries are well demonstrated.

The catheter at times was observed to enter the left ventricle. When this occurred, a forceful systolic impulse was transmitted through the catheter to the operator's hand. If such did occur, the catheter was merely withdrawn under fluoroscopic visualization to a point just above the aortic sinus (Valsalva) and pushed forward toward the aortic valve until the characteristic resistance was felt and the buckling of the catheter was seen. When the catheter did enter the left ventricle, it was often due to excessive force used in passing it against the resistance offered by the aortic valves. In certain positions of the catheter, even considerable pressure fails to overcome this resistance and the catheter chooses to buckle rather than enter the ventricle. One should guard against making undue pressure against the aortic valves since a cusp thus may be injured or ruptured, although no evidence of this was seen in

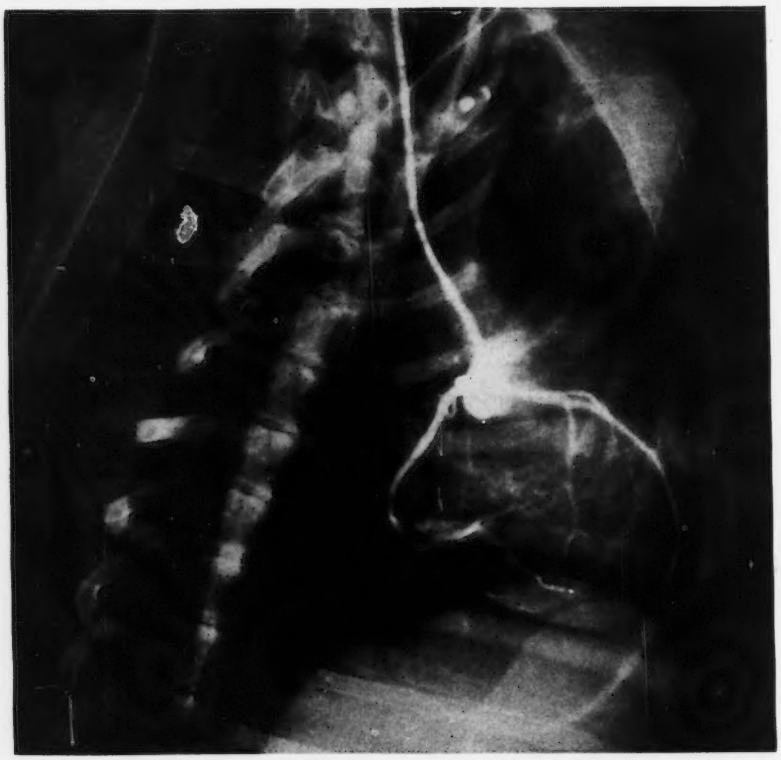

FIG. 2.—Dog. Intact chest. Right side down. Special arterial catheter inserted to aortic sinus through carotid artery. Only 4 cc. of 70 per cent diodrast injected. The left anterior descending and left circumflex coronary arteries and their finer branches are well outlined. The proximal portion of the right coronary artery is obscured behind the left anterior descending artery, but soon appears as a separate shadow.

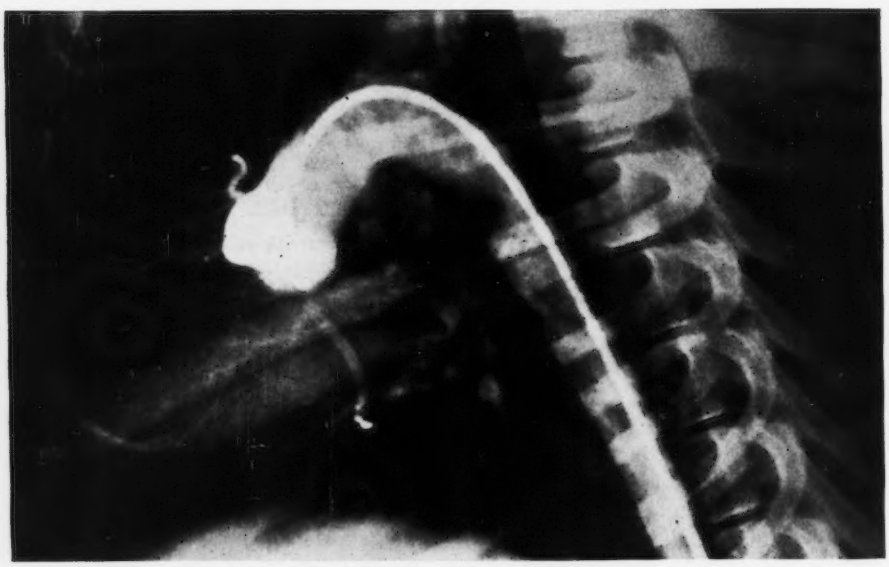

FIG. 3.—Dog. Intact chest. Lateral exposure, right side down. Special catheter inserted through left femoral artery to aortic sinus. Four cc. of 70 per cent Diodrast injected. The left circumflex, left anterior descending and right coronary arteries and their smaller branches are well demarcated, and show good contrast. One also sees the aortic sinus (Valsalva), the separate shadows of all three aortic cusps, the ascending aorta, the aortic arch with the carotid arteries arising from it, and the descending thoracic aorta.

two excised hearts previously subjected to this trauma. If one desires to pass the catheter into the left ventricle, patient, gentle manipulation will affect its entry through the aortic valve without injury.

with many of the fine terminal branches clearly visible. Such pictures were obtained only by lateral exposures. In antero-posterior exposures, the individual coronary arteries were obscured partially by the shadows of the vertebral

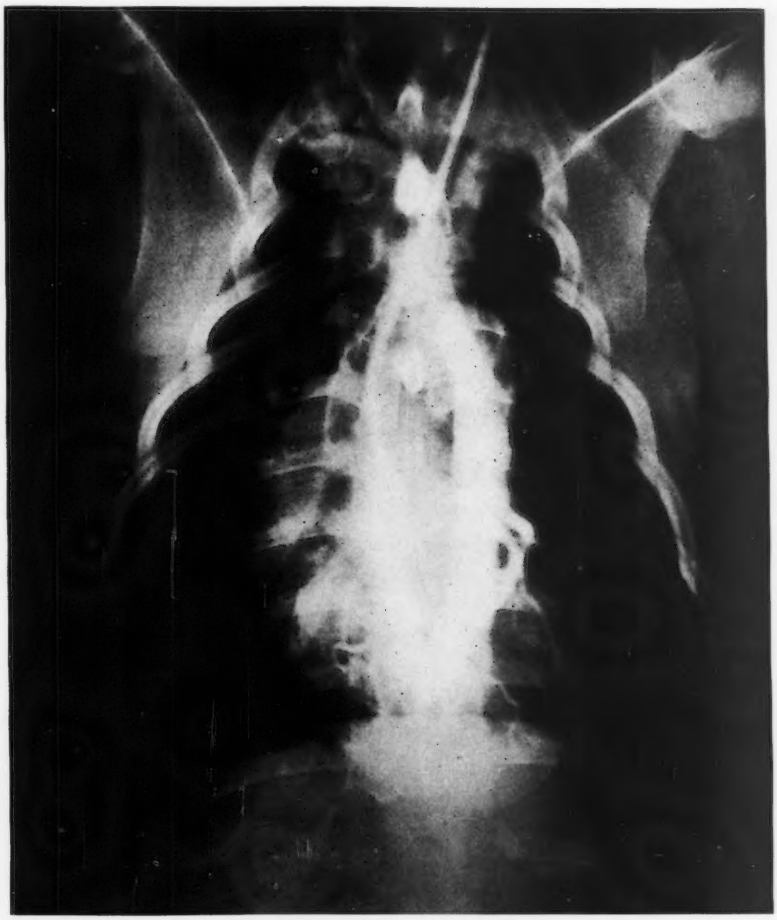

FIG. 4.—Dog. Antero-posterior projection. Four cc. of 70 per cent Diodrast injected through the special arterial catheter which had been passed to the aortic sinus through the carotid artery. The left main coronary artery, its circumflex and anterior descending branches, and their smaller ramifications are well demonstrated, but much detail is lost because of the superimposed shadow of the vertebral column, ribs and thoracic aorta. Compare this view with figure 1, taken with the same subject in lateral projection.

The coronary arteriograms obtained by this method showed the course of the right, left anterior descending, and left circumflex coronary arteries. Each one was outlined individually against the background of the cardiac shadow,

column, and the projection of one coronary vessel upon another (fig. 4). Good coronary arteriograms have been obtained, also, with the animal on its right side, but those taken with the animal on the left side appeared better.

We are attempting by means of numerous coronary arteriograms already taken, in normal animals, to establish the basic normal coronary vascular pattern and its normal variations. In a few instances, we have compared the coronary arteriograms taken on the living dog with roentgenograms of the same vessels injected after death by means of the Schlesinger technique. As the number of normal coronary arteriograms increases, the basic normal pattern, even now quite well established, will become better stabilized and defined.

Experiments are now in progress to visualize in the intact animal coronary arteries previously subjected to experimental lesions.

The development of a safe and dependable method for the roentgenological visualization of the coronary arteries has important implications in respect to the diagnosis and possible treatment of disturbances of the coronary circulation in man, and in experimental coronary artery disease in animals.

Summary

A dependable and apparently safe method for coronary arteriography is described which uses a specially devised catheter inserted into the aortic sinus through a peripheral artery. Clear-cut images of the coronary circulation of living dogs were regularly obtained by this method. Electrocardiograms taken during the procedure showed no abnormalities.

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Heparin in Experimental Myocardial Infarction

By NORMAN B. ROBERG, M.D., AND WILLIAM H. REQUARTH, M.D.

Heparinization, started one hour following coronary ligation, was maintained for twenty-four hours. One week after recovery the hearts were perfused in vivo with india ink. After clearing, the proportion of ventricular mass infarcted was determined. No appreciable difference from the control series was found.

SOLANDT and Best[1] found that coronary artery thrombosis, and consequent myocardial infarction, did not occur in 11 of 12 dogs when a sclerosing solution was introduced into a segment of coronary artery after beginning a twenty-four-hour period of heparinization. The influence of heparinization upon the extent of myocardial infarction following coronary artery occlusion was not determined. During the course of this study it was noted that the excellent reports by Beattie and associates,[2] Blumgart and co-workers,[3] and Le Roy and Nalefski[4] indicated that dicumarol therapy, started postoperatively, had no appreciable effect upon the nature or extent of myocardial infarction following coronary artery ligation. Blumgart used heparin early postoperatively, in addition to dicumarol, in 3 dogs and noted no difference in the reaction of these dogs from that of dogs receiving dicumarol alone. There has been no published study of the effect of heparinization, maintained during the immediate postocclusion period, upon the extent of myocardial infarction; this constitutes the present study.

PROCEDURE

To approximate clinical conditions and to allow early thrombosis in the surgical wound, constant intravenous injection of heparin was started one hour after ligation of the anterior descending branch of the left coronary artery. Dogs weighing 5 to 10 Kg. were operated on, using morphine and Nembutal anesthesia and intratracheal air or 100 per cent oxygen. The artery was dissected free near its origin and ligated. The pericardium was not sutured before closure of the wound. Short lengths of Vinylite tubing were tied into the cephalic and caudal ends of a divided external jugular vein to facilitate both the removal of blood to determine clotting time and the infusion of heparin. The dosage of heparin recommended by Solandt and Best[1] was followed: an initial dose of 0.45 mg. per Kg. of body weight and a maintainance dose of 0.35 mg. per Kg. per hour. The heparin was diluted to 0.02 per cent in physiologic saline solution. Clotting time was determined by allowing 1.0 cc. of blood to drop from the Vinylite cannula into a clean, saline-rinsed glass tube of 25- by 10-mm. capacity. Definite loss of fluidity, rather than clot formation, was taken as the end point. The clotting time was maintained usually at thirty to sixty minutes, the control readings varying from five to ten minutes. The clotting times were often erratic, frequently rising unexpectedly to from one hundred twenty to one hundred eighty minutes about eight hours after the infusion was started. Fatal intrathoracic hemorrhage usually occurred when such prolongation of clotting time was present, and also occurred when the prescribed dosage was exceeded because the clotting time apparently was below thirty minutes. The dogs were kept lightly narcotized with intravenous Nembutal, and the infusion of heparin was maintained for twenty-four hours. After one week without medication, the dogs were sacrificed under morphine-Nembutal anesthesia. The sternum was split, the superior and inferior venae cavae were clamped, and, as the heart began to collapse, the aorta was clamped. Following the

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procedure of Wearn,[5] 25 to 50 cc. of 50 per cent india ink in distilled water were injected into the left ventricular cavity, followed by 5 mg. of histamine base. The heart was stopped with fair promptness by the intraventricular injection of 10 cc. of 10 per cent formalin. Wearn's technic of perfusing the excised heart gave better filling in normal hearts, but this procedure was abandoned because of the difficulty in maintaining vigorous beating in hearts which had undergone coronary ligation and myocardial infarction. With the perfusion by india ink, the myocardium turned black except for the area of infarction, which was whitish-gray. Inasmuch as the integrity of the capillary circulation is the final determinant of circulatory adequacy, the obliteration of the capillary bed as demonstrated by perfusion with india ink was considered indicative of the extent of myocardial infarction. The hearts were fixed in 10 per cent formalin after the auricles and great vessels had been dissected away. The hearts were then cleared by the method of Spalteholz.[6] After clearing, the area of infarction was highly translucent, the remainder of the myocardium being opaque. A bright light was held within the left ventricular cavity and the irregularly infarcted area was cut out. The weight of the ventricles and of the infarcts was determined, and the percentage weight of ventricular muscle which had been infarcted was computed.

Results

One hundred and two dogs were operated upon. Thirty-two (31.5 per cent) died during or within minutes of coronary ligation. Twelve (11.8 per cent) died in the first two hours. Ten (9.8 per cent) died with massive intrathoracic hemorrhage during the twenty-four-hour period of heparinization. Five (4.9 per cent) died during heparinization without gross evidence of hemorrhage. Only 4 dogs (2 with heparin, 2 controls) died between the second and seventh days. Of the 39 surviving dogs, in 13 the hearts were discarded because of uncertainty as to the ligation of the entire descending branch of the left coronary artery, because of injury to, or ligation of, the accompanying veins, or because of poor perfusion. Fourteen hearts remained as satisfactory controls, and 12 as satisfactory trials with heparinization. The weight of the infarcted areas, expressed as percentage of the total weight of both ventricles before removal of the infarcted area, was as follows:

Controls (per cent)		Heparin series (per cent)
10.8		5.2
11.5		9.1
13.0		9.8
13.2		10.1
13.4		12.7
15.4		13.8
15.8		15.4
18.0		16.6
18.0		18.6
19.7		20.8
21.5		22.2
26.7		23.5
28.4	Average	14.8
28.6		
Average 16.7		

The small difference between the two series of experiments is not considered to be significant.

Conclusion

Heparinization of dogs, starting one hour after ligation of the anterior descending branch of the left coronary artery, and maintained for twenty-four hours, had no appreciable effect upon the extent of the myocardial infarction.

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Preliminary Report on the Clinical Use of a New Anticoagulant, Phenylindandione

By Ancel U. Blaustein, M.D., James J. Croce, Jr., M.D., Marie Alberian, B.S., and Neil Richey, M.T.

Heparin and dicumarol are both useful drugs but each has its limitations and accordingly search goes on for newer drugs that lack some of these limitations. A new anticoagulant, phenylindandione produces a prothrombopenia more rapidly than dicumarol and its catabolism is equally more rapid. This, therefore, aroused interest in clinical trials utilizing this new prothrombopenic agent. The drug is a light yellow, crystalline compound put up in tablet form and administered by mouth.

In 1944, Kabat, Stohlman, and Smith[1] described the effect of certain indandione derivatives on prothrombin levels in animals. In 1947, Soulier and Guegen[2] utilized a substance called phenylindandione clinically as an anticoagulant. Jaques[3] has recently stimulated interest in this latter substance by his observations that its administration to dogs resulted in the production of hypoprothrombinemia more rapidly than did the administration of dicumarol. He carried out studies to investigate the possible mechanism of its behavior, since vitamin K is without effect on the action of this drug, and to observe toxic manifestations, if any.

This preliminary report deals with clinical trials of phenylindandione under controlled conditions on 20 patients. The investigation centered upon establishment of dose levels, frequency of administration, speed of action and recovery, individual responses, and possible toxicity. Sedimentation rates, platelet counts, and white blood cell differential counts were determined and liver function tests and urinalyses were performed before and after administration of the drug, in an effort to ascertain any alteration in these values referable to the use of this new anticoagulant.

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This work was supported in part by a grant from the Charles Frosst Company, Montreal, Quebec, who also kindly supplied us with the phenylindandione (Danilone).

Materials and Methods

Fifty-three hospitalized patients, 47 of whom had thrombotic episodes prior to administration of the drug, were the subjects of this study. Sixteen of them had acute coronary thrombosis, 17 postoperative phlebitis, 5 acute idiopathic thrombophlebitis, 1 recurrent thrombophlebitis, 1 postpartum thrombophlebitis, 1 aortic thrombosis, 1 mesenteric thrombosis, 1 subacute bacterial endocarditis, 4 pulmonary infarction, 1 popliteal aneurysm, and 1 patient suffered from cerebral thrombosis. Four patients were treated prophylactically.

1. Prothrombin concentration was determined by the one-stage modified Quick method.
2. The Westergren method was used in estimating the sedimentation rate.
3. Platelet counts were made by the Rees and Ecker method.
4. The Lumetron colorimeter was used in performing liver function tests.
5. Bromsulfalein excretion was estimated by the Rosenthal method.

Dosage

Initial Dose. The initial dose used was arrived at by the trial-and-error method. To Patient E.G., following determination of his prothrombin time, 50 mg. of phenylindandione were given by mouth; after four hours the prothrombin time was again determined. The prothrombin concentration was depressed only 5 per cent in that period of time; therefore 100 mg. were given at bedtime. The following morning the prothrombin concentration had dropped to 40 per cent activity and by afternoon to 25 per cent activity. The initial prothrombin concentration was 65 per cent and the drop to 25 per cent occurred in twenty-three and one-half hours, after a total of 150

mg. had been given. Thirty-one of the remaining patients were given 150 mg. as the total initial twelve-hour dose; some received 50 mg. in the morning and 100 mg. at night, while others received their dosage in the reverse order. This reversal of order did not seem to affect the time required to reduce the prothrombin concentration.

Patient R. H. was given 50 mg. on the first day and 100 mg. the second day; forty-three and one-half hours elapsed before the prothrombin concentration dropped from 90 per cent to 30 per cent.

Patient A. G. received an initial dose of 175 mg. and twenty-nine and one-third hours later the prothrombin concentration had dropped from 100 to 25 per cent activity; forty-six hours after the initial dose, the prothrombin time was infinity. This procedure was repeated in Patient L. S. to verify the lack of control that resulted from the added dosage. She received 100 mg. in the morning and 100 mg. at night. Twenty-eight hours later the prothrombin activity had changed from 100 to 25 per cent; forty-seven hours later the prothrombin time was infinity. Therefore, it was felt that 150 mg. represented an optimum safe, adequate, dosage level, and in the case of Patient R. H. it was felt that the initial dose of 50 mg. was inadequate. One patient, L. B., required 500 mg. before his prothrombin activity was depressed from 100 to 30 per cent. We have since tried an initial dosage of 200 mg. in 16 succeeding cases and have concluded that this is more in keeping with the proper initial dosage in a man or woman weighing about 150 pounds. With this dosage the desired level was obtained within 24 to 36 hours and the prothrombin times did not go to infinity.

Frequency of Administration. As in dicumarol therapy the maintenance dose has to be gauged by the daily prothrombin time, and the level to which one cares to lower the prothrombin activity is arbitrary. Some believe that there is no therapeutic effect if a level of 10 per cent activity is not achieved, while others claim a level of 30 to 40 per cent is adequate. In this series, 30 per cent of activity was the point at which administration of the drug was stopped, and if the concentration rose above it, 50 mg. of phenylindandione were given. The average daily dosage other than the initial dose in 53 of the patients was 65 milligrams.

Table 1 gives the results of phenylindandione administration in 20 patients who had been treated when this article was first prepared for publication; table 2 gives results in 33 subsequent patients. Administration varied, from case to case, from 50 to 140.6 mg. per day except in two instances where 25 mg. or less per day was the daily requirement. These 2 patients had major bowel resections. In view of the wide swings we noted in the daily prothrombin times, it was felt that the daily maintenance dose ought to be split in two in order to maintain a sustained prothrombin level. We did this in our last 15 patients and found that the prothrombin time varies much less from day to day.

Results

Speed of Action and Recovery. In 18 cases the desired prothrombin level was reached in from 10 to 20 hours. In 20 cases it was reached from 20 to 28 hours later. In 7 cases it was reached in from 29 to 40 hours. In 3 cases the level was reached from 40 to 50 hours later. Patient L. B. required 500 mg. before the prothrombin activity changed from 100 per cent to 30 per cent in a period of seventy-two hours. This could be interpreted only as the same type of variation one often sees with dicumarol. In Patient L. R. it took forty-eight hours for the prothrombin activity to reach a level of 25 per cent from an initial level of 100 per cent. The initial dose of this latter patient was 150 mg., as was that of Patient L. B. In 4 cases, 500 mg. was required in order to obtain the desired effect. However, an initial dosage of 200 mg. seems to prolong the prothrombin time to clinically effective levels more rapidly.

The average time taken for the prothrombin concentration to return to its initial value was forty-eight hours, and there was little discrepancy noted in the rate of recovery.

Individual Responses and Toxicity. Jacques[3] observed bleeding in only 2 dogs of his series in which prothrombin times of infinity were reached and, therefore, overdosage established. One of these dogs had received antidistemper serum at the same time the phenylindandione

was administered and the other had a superficial infection. Three of our patients received doses that led to prothrombin times of infinity and one of these, Patient C. L., had hematuria which appeared only on one occasion and never recurred. He had no other signs of bleeding and cessation of the drug for forty-eight hours resulted in a return of the prothrombin activity to normal levels. Patient L. S. received 200 mg. in twelve hours and cessation of the drug in her case led to a return of the prothrombin activity to normal. The third patient, A. G., whose prothrombin activity reached infinity on an initial dose of 175 mg., did not show any signs of bleeding or have any other toxic manifestations. Patient G.D. had a slight nosebleed on the fourteenth day of administration of the drug and the prothrombin concentration on that day was 35 per cent. Up to that time he had received a total of 700 mg. of phenylindandione. Soulier and Guegen[2] reported renal damage following very large doses of the drug, presumably due to deposition of the crystals in the tubules. Casts were observed in the urine of a dog receiving 50 mg. per kilogram of body weight per day on the twenty-third day of the experiment; no casts were seen in the urine of animals given smaller doses. Soulier and Guegen also observed dryness of the mouth, polydipsia, polyuria, and sometimes tachycardia after the administration of 10 and 20 mg. per kilogram of body weight per day to their patients; 2 of the patients had a brief scarlatiniform rash. We did not observe any of these toxic manifestations in our 53 patients.

We did encounter the phenomenon of what we must call resistance for lack of a better term. In one patient, H. P., we were asked to cease administering the anticoagulant prior to the onset of her menses. We allowed her prothrombin time to return to normal and one week later we attempted to reinstitute therapy but without avail. Over a period of seven days we administered 600 mg. of the drug without appreciably altering the prothrombin time. In one case, M. L., we gave 150 mg. each day for four days and the prothrombin time was prolonged only from a normal of 12 seconds to 18 seconds, which we considered clinically ineffective. A third case, E. B., showed an unusual phenomenon in that we were able to prolong his prothrombin time to clinically effective levels but, despite daily increase of the dosage, the prothrombin time dropped back to normal and remained at normal levels.

Effect on Liver Function. The following determinations were made before and one week after administration of the anticoagulant: blood sugar, blood cholesterol, total protein, serum albumin, serum globulin, serum fibrinogen, hippuric acid synthesis, icteric index, van den Bergh reaction, and bromsulpthalein excretion. No significant changes could be detected in these values.

Urinalyses. These were made daily in order to check the urine for any evidence of bleeding, crystal deposition, or casts. At no time was there interference with urine output. Bloody urine was noted in Patient C. L. on the second day after phenylindandione administration when his prothrombin time was infinity. Phenylindandione and its excretion products do not appear to interfere with the reaction of Benedict's test for sugar in the urine.

Effect upon the Sedimentation Rate and Platelet and White Cell Differential Counts. In 6 of our patients the blood sedimentation rate was determined and platelet and white cell differential counts were made before phenylindandione administration. Following its administration, when the prothrombin concentration reached a level of 30 per cent, the procedures were repeated at the same hour of the day and under the same conditions as those existing when the initial values were determined. No significant alterations of the values could be detected.

Conclusions

In this preliminary report with observations made on 53 patients, it appears that the new anticoagulant, phenylindandione, if used cautiously could meet the need of clinicians for an anticoagulant intermediate in action between heparin and dicumarol, resembling dicumarol more closely than heparin in its behavior. An initial dose of 200 mg. is adequate. Fifty mg. the first day followed by 100 mg. the second day are inadequate. The average daily maintenance

TABLE 1.—*Results of Phenylindandione Therapy in Twenty Patients*

Patient	Sex	Age	Diagnosis	Initial Dosage	Frequency of Administration	Rate of Depression of Prothrombin Activity	Rate of Return to Original Prothrombin Level	Total Dose	No. of Days on Therapy	Individual Reaction or Signs of Toxicity	Clinical Effects
		(years)		*(mg.)*	*(mg. per Day)*		*per cent; (in) hours*	*mg.*			
1. E. G.	M	38	Postoperative phlebitis (left leg)	150	50	65–25% in 23.3 hr.	65; 47	500	20	None	Uneventful recovery
2. G. M.	M	47	Coronary thrombosis	150	45.8	90–30% in 28 hr.	90; 43	700	16	Slight nosebleed 14th day of administration, which ceased when drug was discontinued	Uneventful recovery; no repetition of thrombosis while on the anticoagulant
3. W. D.	M	45	Coronary thrombosis	150	56	65–30% in 28.5 hr.	65; 47	1000	16	None	Uneventful recovery
4. R. H.	M	49	Coronary thrombosis	50	50	90–30% in 43.5 hr.	90; 41	500	13	None	Recurrent attack one month later. Patient was not on maintenance dosage
5. L. R.	F	44	Postoperative phlebitis (right leg)	150	55	100–25% in 32.5 hr.	100; 49	550	10	None	Pain disappeared within 4 hr. Phlebitis cleared up in 48 hr.
6. A. G.	F	32	Postpartum phlebitis (right leg)	175	50	100–25% in 23⅔ hr.	100; 51	500	5	None	Uneventful recovery
7. L. S.	F	61	Thrombophlebitis (right leg)	200	—	100–25% in 28 hr.	100; 49	800	10	None	Uneventful recovery
8. C. L.	M	43	Coronary thrombosis	100	—	100% to infinity in 26 hr.	100; 54	500 dicumarol; 700 Danilone	16	Hematuria one day when prothrombin time was infinity	Uneventful recovery
9. L. B.	M	56	Postoperative prophylaxis	150	50	100–30% in 72 hr.	100; 50	500	6	It took 500 mg. to depress the prothrombin concentration from 100–30%	Uneventful recovery

10. H. P.	F	41	Coronary thrombosis	150	57	100–25% in 26.5 hr.	100; 48	950	15	None	Daily dosage was stopped with onset of menses. When resumed over 500 mg. were necessary to bridge the prothrombin concentration 10%
11. W. A.	M	84	Postoperative prophylaxis	150	50	100–35% in 28 hr.	100; 48	250	3	None	Uneventful recovery
12. J. M.	M	74	Postoperative prophylaxis	150	50	65–30% in 28 hr.	100; 47	200	3	None	Uneventful recovery
13. H. D.	M	65	Postoperative prophylaxis	150	50	75–30% in 28 hr.	100; 46	250	3	None	Uneventful recovery
14. A. L.	F	31	Postpartum phlebitis	150	50	100–30% in 27.5 hr.	100; 48	500	5	None	Uneventful recovery
15. D. M.	F	81	Thrombophletitis	150	50	100–30% in 28 hr.	100; 47	500	5	None	Uneventful recovery
16. V. D.	F	28	Thrombophlebitis	150	50	75–25% in 28 hr.	100; 46	350	7	None	Pain disappeared 5 hr. after administration; tenderness and increased warmth disappeared in 24 hr.
17. W. C.	M	54	Coronary thrombosis	150	44	90–30% in 20 hr.	100; 52	400	10	Rapid decrease in prothrombin concentration: 90–17% in 24 hr.	Feels well
18. H. R.	M	47	Coronary thrombosis	150	50	75–30% in 28 hr.	100; 45	850	13	None	The time the patient states he felt best corresponded to the lowest prothrombin concentration reading
19. M. G.	M	49	Coronary thrombosis	150	50	90–30% in 28 hr.	100; 46	700	10	None	This was a recurrent attack—recovery good
20. R. G.	M	46	Coronary thrombosis	150	50	80–30% in 28 hr.	100; 46	800	12	None	This was a recurrent attack—recovery good

TABLE 2.—*Results of Phenylindandione Therapy in Thirty-Three Patients*

Patient	Sex	Age	Diagnosis	Initial Dosage	Frequency of Administration	Rate of Depression of Prothrombin Activity	Return to Normal Level[a]	Total Dose	No. of Days on Therapy	Individual Reaction or Signs of Toxicity	Clinical Effects
		years		*mg.*	*mg. per day*		*hours*	*mg.*			
21. J. G.	M	35	Poss. myocardial infarction. Anginal syndrome	150	75	24 hours 2 × normal	30	375	4	none	Uneventful. Drug stopped because patient proved not to be myocardial infarction
22. M. C.	M	59	Anterior wall myocardial infarction	150	125	48 hours 2 × normal	36	2500	23	none	Pt. difficult to raise to adequate level. Once at level, well maintained on 125 mg. of Danilone daily
23. M. B.	M	60	Poss. myocardial infarction	150	61.5	18 hours 2 × normal	42	950	14	none	Uneventful
24. W. B.	M	76	Mesenteric thrombosis	150	29.7	14 hours 3 × normal	38	625	17	none	Postop. mesenteric thrombosis, 16 inches of jejunum resected at operation. Pt. started on drug immediately postop. Made uneventful recovery. No hemorrhage in spite of level up to 5 times normal on 5th postop. day. Liver function tests showed reverse A/G ratio
25. A. S.	M	46	Posterior wall myocardial infarction	150	113.9	24 hours 1.7 × normal	24	1175	10	none	Pt. transferred to hospital nearer his home when he was able to be moved. Pt. required considerable Danilone—somewhat resistant
26. A. J.	F	39	Rt. thrombophlebitis; pulmonary infarction	200	75	24 hours 2 × normal	32	775	9	none	Danilone, aureomycin and penicillin were used. Uneventful recovery
27. F. D.	M	63	Carcinoma of urinary bladder—recurrent thrombophlebitis	150	43.7	24 hours 2½ × normal	43	325	5	none	Rapid recovery—same effect in previous attacks with dicumarol

28. R. C.	M	56	Aortic thrombosis; postop. aortectomy	150		18 hours 2 × normal	†	150	1	†	Postop. aortectomy for aortic thrombosis. Bilateral lumbar ganglionectomy. Pt. died in cardiac failure 4th day postop., 1st day of therapy
29. I. Z.	M	45	Acute thrombophlebitis, urticaria	200	59.4	10 hours 2 × normal	‡	675 in hosp.	9	none	Pt. admitted with acute thrombophlebitis and urticaria, presumed to be caused by penicillin. Discharged on 9th hospital day and is being followed with weekly prothrombin time as an out-patient
30. J. L.	M	49	Postop. gastrectomy for carcinoma of stomach; pulmonary infarction	150	20.8	20 hours 3 × normal	40	275	6	none	Pt. debilatated—responded readily to drug; uneventful recovery
31. K. B.	F	53	Subacute bacterial endocarditis—cerebral embolus	150	51.2	18 hours 2 × normal	28	1225	22	Some purpuric skin lesions	Pt. suffered cerebral embolus in course of subacute bacterial endocarditis; recovery poor
32. E. B.	M	59	Poss. myocardial infarction	150	116.7	18 hours 1½ × normal	8	1500	13	none	Pt. signed release—no follow-up. Before he left, stopped drug; showed resistance
33. C. S.	M	74	Thrombophlebitis; coronary insufficiency	150	85.7	36 hours 2 × normal	39	750	7	none	Uneventful
34. M. L.	M	35	Posterior wall myocardial infarction	150	150	24 hours 1.4 × normal	—	750	5	none	Pt. resistant. Removed to Psychiatric Inst. before any studies could be done
35. J. B.	M	66	Arteriosclerotic peripheral vascular disease	200	50	18 hours 2 × normal	—	450	6 days in hosp.‡	none	Pt. to continue drug as out-patient
36. A. T.	F	34	Postop. hysterectomy; poss. pulmonary infarction	200	58.3	36 hours 2 × normal	36	650	4	none	Sudden post-chest pain, cyanosis, 2nd postop. day; cause undetermined

TABLE 2.—*Continued*

Patient	Sex	Age	Diagnosis	Initial Dosage	Frequency of Administration	Rate of Depression of Prothrombin Activity	Return to Normal Level[a]	Total Dose	No. of Days on Therapy	Individual Reaction or Signs of Toxicity	Clinical Effects
		years		*mg.*	*mg. per day*		*hours*	*mg.*			
37. N. B.	M	63	Posterior wall myocardial infarction	200	120.3	24 hours 2 × normal	—	925	8	none	Uneventful
38. H. K.	F	38	Postpartum thrombophlebitis	150	131.4	30 hours 2 × normal					Out-patient
39. J. P.	M	53	Postop. hemorrhoidectomy; thrombophlebitis	200	125	52 hours 2 × normal	42	2825	21	none	Uneventful recovery, resistant to small dosage of Danilone.
40. C. L.	M	73	Cerebral thrombosis and thrombophlebitis	200	22.2	16 hours 2½ × normal	—	400	10	none	Patient died—cause of death undetermined
41. J. P.	M	67	Posterior wall myocardial infarction	200	140.6	48 hours 2 × normal	32	2450	17	none	Patient made uneventful recovery—resistant to small dosage of Danilone
42. W. D.	M	70	Anterior wall myocardial infarction	200	120.8	32 hours 2 × normal	30	2375	19	none	Uneventful recovery
43. M. W.	F	46	Carcinoma of uterus with metastases; thrombophlebitis postop.	250	25	18 hours 4½ × normal	32	450	9	uterine bleeding?	Drug stopped because vessels of leg were found to be occluded by carcinoma; uterine bleeding present before and after administration of drug. Uterine bleeding continued after drug was discontinued
44. J. D.	M	28	Postop. hernia; thrombophlebitis	200	50	14 hours 2½ × normal	—	300	3	none	Patient signed release
45. M. C.	F	70	Arteriosclerotic heart disease; thrombophlebitis	200	97.5	30 hours 2 × normal	—	725 in hospital	7	none	Uneventful recovery. Patient being continued on drug as an out-patient

46. L. H.	F	66	Carcinoma of the stomach—subtotal gastrectomy; postop. thrombophlebitis	200	21.4	16 hours 2½ × normal	41	350	9	none	Good recovery
47. R. M.	M	62	Prostatectomy; postop. thrombophlebitis	200	60.7	18 hours 2 × normal	—	1050 to date	15 to date	none to date	Patient still being treated. Response to therapy fair
48. W. W.	M	62	Popliteal aneurysm	200	73.5	24 hours 2 × normal	—	1450 to date	18 to date	none to date	Patient operated upon while under therapy without undue bleeding—still under therapy
49. A. S.	F	35	Gastrectomy for peptic ulcer; postop. pulmonary infarction	150	11.1	10 hours 3 × normal	—	250 to date	10 to date	none to date	Patient making uneventful recovery—still under therapy
50. G. N.	F	57	Nephrectomy; postop. thrombophlebitis	200	50	12 hours 2 × normal	—	600 to date	9 to date	none to date	Results of therapy fair to date
51. M. C.	F	48	Thrombophlebitis	200	82.1	38 hours 3 × normal	—	775 to date	8 to date	none to date	Results fair. Possible extension of thrombophlebitis in spite of therapy
52. E. W.	F	74	Cerebral thrombosis	200	58.3	18 hours 2 × normal	—	550 to date	7 to date	none to date	Recovery good to date
53. J. B.	M	51	Postprostatectomy thrombophlebitis	200	58.3	16 hours 2 × normal	—	375 to date	3 to date	none to date	Too early to evaluate therapy

* — indicates return time was not determined.
† The patient died.
‡ Continued as out-patient.

dose in 53 patients was 65 milligrams. The speed of action of the drug varied. In 38 of the 53 patients to whom the drug was administered it took twenty-eight hours or less to reach levels of 25 to 30 per cent of activity. It took on an average of forty-eight hours for the prothrombin concentration to return to its original level. Bleeding episodes occurred in 2 patients. One patient, C. L., had, without our knowledge, been given 500 mg. of dicumarol prior to receiving 100 mg. of phenylindandione. The second patient, G. M., had received an initial dose of 150 mg. and had a nosebleed on the fourteenth day of treatment. No effect upon liver function could be detected by means of the series of tests that were used. The sedimentation rate, platelet count, and white blood cell differential count do not appear to be altered by the anticoagulant.

No dogmatic statements can be made, but it is hoped that this report will stimulate further interest in this new anticoagulant.

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Dicumarol Fatality in Severe Hypertensive and Arteriosclerotic Cardiovascular Disease Despite Controlled Therapeutic Level

By Rose E. London, M.D.

The following case demonstrates fatal widespread hemorrhage resulting from the use of dicumarol at what is ordinarily considered a safe and desirable therapeutic level. It is suggested that the accompanying severe hypertensive and arteriosclerotic cardiovascular disease may have injured the contiguity of the vascular tree to such an extent that active diapedesis occurred in the presence of dicumarol.

SINCE dicumarol was introduced into clinical use in 1941, numerous articles have been published emphasizing its beneficial effects in the treatment and prevention of coronary thrombosis, thrombophlebitis, and thrombosis of the retinal veins. While the incidence of toxic effects has been claimed to be slight under careful laboratory observation of the prothrombin time, there have been reported approximately twenty-three deaths due to dicumarol up to the present time.[1] These reports emphasize the serious effects due to self medication, lack of careful observation, and complicating factors, such as liver or kidney damage, blood dyscrasias, severe hypertension, recent operations on the brain and spinal cord, ulcerative lesions of the gastrointestinal tract, obstetrical cases near term, and subacute bacterial endocarditis. In the reported fatal cases it was generally found that either critical or unsafe levels existed as a result of overmedication or lack of control, or that intrinsic defects were present that would cause bleeding.

The following case of dicumarol fatality is presented for two reasons. First, it illustrates the disastrous complications of the drug in spite of control at recommended therapeutic levels in an elderly patient with severe hypertensive and arteriosclerotic cardiovascular disease. The method of prothrombin time determination in this case was the standard Quick method for which the therapeutic level of 30 to 50 seconds is considered desirable and safe.[2] Second, it serves to emphasize the danger of a false sense of security in patients treated with a dangerous drug over a long period of time. In this case the patient had been controlled on similar dosage for a period of seven months without serious complications.

From the Department of Medicine, St. Francis Hospital, Miami Beach, Fla.

Case Report

Mrs. D. T., a 70 year old white woman, was seen for the first time January 28, 1949, complaining of palpitations. She had always been in good health, had four normal pregnancies, and led a strenuous life of work until twenty-five years ago when she was discovered to have hypertension, which remained "above 190" on repeated examinations. For nineteen years she had frequent attacks of rapid heart action and weakness and had been receiving digitalis over the past fourteen years for shortness of breath and fatigue. Four years ago an encapsulated carcinoma of the right breast was enucleated.

In July 1948 the patient had an attack of weakness in the left arm and leg associated with stupor. During hospitalization in another city, dicumarol therapy was started for the first time and was given continuously in constant dosage of 50 and 100 mg. on alternate days. Prothrombin time was said to be well maintained, except on one occasion when transient hematuria appeared. She continued on the same dosage of dicumarol for about one month after she had left the care of her previous physician.

At her first visit on January 28, 1949, the patient complained of palpitations during the preceding twelve hours, without dyspnea or chest pain. Physical examination revealed a well-preserved, alert, 70 year old woman in no acute distress, not dyspneic or cyanotic. Examination of the head and neck revealed no abnormality except for the fundi which

showed irregularity and tortuousity of the vessels with normal discs. There was a small scar on the right breast, but no masses were felt in either breasts or axillae. The lungs were clear to percussion and auscultation. The heart was moderately enlarged with the point of maximal impulse in the sixth intercostal space, outside the midclavicular line. The sounds were of fair quality. There was a totally irregular rhythm with a ventricular rate of 120 and a pulse rate of 100. A rough systolic murmur was heard over the base, but no thrills were present. The blood pressure was 220/120.

Abdominal examination showed no abnormality. Neurologic examination revealed equal strength in both arms and legs but a slight lag in rapid, rhythmic, alternating movements of the left hand and increase in tendon reflexes of the left biceps, triceps, knee, and ankle. A positive finger-stretch reflex was present in the left thumb, and the abdominal reflexes were absent bilaterally. Cranial and sensory nerves were intact. The extremities showed no edema.

Fluoroscopy of the chest revealed normal movement of the diaphragm and slight increase in pulmonary markings. The roentgenograms revealed a generalized increase in pulmonary markings and a generalized increase in the size of the heart with blunting of the apex and enlargment of the left ventricle. The aorta was markedly elongated, widened, calcified, and tortuous.

The hemoglobin was 15.5 grams (92 per cent) and the white blood cells numbered 7,750. Urine was normal except for a 1+ albumin reaction.

The rapid heart rate and pulse deficit subsided satisfactorily with increase in the dose of digitoxin and the patient was advised to discontinue taking dicumarol since she refused adequate laboratory follow-up. However, one month later, the patient's previous physician visited her and on Feb. 29, 1949, again started her on the same dosage of dicumarol as employed on prior treatment. Her prothrombin time on March 8, 1949, was 70 per cent of normal or twenty seconds (normal sixteen seconds) on alternate doses of 50 and 100 mg. daily. Her dose was increased to 100 mg. a day, and one week later the prothrombin time was 38 per cent normal or 42 seconds. It was felt that, in her case, less than the usual therapeutic level might be safer and therefore, on March 15, 1949, she was returned to her previous dosage. The following week she did not appear for her weekly prothrombin test, but on March 28, 1949, she returned, complaining of vague discomfort in the epigastrium, associated with anorexia and frequency of urination of forty-eight hours' duration. Physical examination revealed no change from the previous conditions, but a urinalysis showed 10 to 20 red blood cells and 2 to 5 white blood cells per high-power field. Dicumarol was therefore permanently discontinued.

On the following day, March 29, the patient developed increasingly severe precordial pain. A half hour later she was found to be in extreme pain, acutely ill, pale, cyanotic, and sweating. Over the following fifteen minutes the blood pressure dropped from 220/110 to 120/80. There was no sign of cardiac failure. The ventricular rate was 110 and irregular, with a pulse rate of 88. The patient was given oxygen, morphine sulfate, and was hospitalized.

Her prothrombin time on admission was forty seconds (control thirteen seconds) and on the following day the nonprotein nitrogen was 53 mg. per 100 c.c. of blood and a blood count revealed 4,200,000 erythrocytes with 13 grams hemoglobin. The leucocytes numbered 18,200 with 83 per cent segmented polymorphonuclear cells (5 stab and 1 juvenile form) and 11 per cent lymphocytes. The Kahn reaction was negative. Urinalysis showed 4+ albumin reaction and 8 to 10 white blood cells and 30 to 40 red blood cells per high-power field. On the following day there was 3+ albumin reaction and 40 to 50 white blood cells with 15 to 20 red blood cells per high-power field and a moderate number of hyaline and granular casts. The electrocardiogram showed auricular fibrillation, left axis deviation, and depression of the RS-T segments in all limbs and chest leads consistent with digitalis effect. There was no evidence of acute myocardial infarction.

Over the following twelve hours the patient gradually lapsed into deep coma. Her blood pressure varied from 80/60 to 120/80 and there was no evidence of cardiac failure. Her urinary output over thirty-six hours was 30 cc. and the nonprotein nitrogen on the third day arose to 83 mg. per 100 cc. of blood. Generalized hypotonicity appeared and there were no localizing signs or involuntary movements. There was no evidence of bleeding from the external orifices, although large ecchymoses surrounded the areas of venipuncture. The patient exhibited intermittent Cheyne-Stokes respiration, gradual rise in temperature, and finally expired on April 1, 1949, seventy-four hours after admission.

Postmortem Examination

*Gross Findings:** External examination revealed the well-nourished body of an elderly white woman with a few ecchymotic areas over the dorsum of the hand and the antecubital fossae, surrounding points of venipuncture. There was no cyanosis, jaundice, or petechial hemorrhages.

Scattered through the root of the mesentery one noticed small hematomas, varying in size from 0.5 cm. to several centimeters in diameter. The peritoneal surfaces were smooth and glistening. The liver and gall bladder were normal. In the tissues surrounding the pancreas was noted a rather diffuse hematoma, which also extended to the pararenal and adrenal areas on both sides. The parenchyma

* The gross and microscopic observations were reported by Dr. Philipp Rezek of the Department of Pathology, St. Francis Hospital.

of the adrenals, however, was grossly normal. The mucosa of the gastrointestinal tract was normal throughout.

The capsule of the kidney stripped with ease revealing a roughly granular cortex with loss of normal corticomedullary demarcations. There were a few 0.5-cc. cystic areas noted within the cortex. The pelves, ureters, and bladder were grossly normal.

The chest was bilaterally symmetrical. The pleural surfaces of the lungs were smooth and glistening. The right pleural cavity contained no free fluid. The left pleural cavity contained a few centimeters of blood-tinged fluid, and at the hilar area of the left lung there was a blackish-red grapefruit-sized mass that lay subpleurally but not in the mediastinum. This mass was found to be a large blood clot, the origin of which was undeterminable since there was no break in the continuity of the adjacent blood vessels; and it was therefore judged to be a hemorrhagic diapedesis. Cut section of the left lung showed a hemorrhage within the parenchyma itself situated approximately 3 or 4 fingersbreadth from the hilar region.

The heart was enlarged, and there was rather extensive pericarditis present, fibrinous in type and fairly recent, allowing for easy stripping of the visceral and parietal pericardial layers. The left ventricle was markedly hypertrophied and the papillary muscles of the left ventricle were thickened. There was a slight thickening of all the heart valves. The myocardium showed no gross evidence of fresh infarction although there was distinct scarring of the left ventricle particularly in the anterior part of the apical area and the upper posterior wall. The endocardium of all four chambers, with special reference to that covering the papillary muscles, showed numerous small and large irregularly shaped fresh hemorrhages varying in size from 0.5 to 1.5 cm. in diameter. Both branches of the left coronary artery showed marked sclerosis and narrowing of their lumina but no thrombosis.

The ascending and thoracic portions of the aorta were markedly sclerotic with atheromatous deposits throughout, the intimal surfaces of which were intact.

Microscopic Findings. The areas of hemorrhage described grossly showed tremendous pools of red blood corpuscles in which were floating remnants of walls of the small vessels, precapillaries and capillaries, and pieces of lymphatic tissue and even of cartilaginous tissue. There were no vascular changes seen within the floating remnants of the vascular tree. The wall of the pulmonary vessels showed thickening and hyalinization with pillow-like protrusions formed by splitting of the elastic fibers. The alveoli had collapsed in some areas and were distended in others with very thin interalveolar septa between.

The muscular layers of the esophagus were surrounded by collections of red blood cells.

Sections of the four chambers of the heart, the papillary muscles, the valvular apparatus, and the interventricular septum as well as the coronary tree showed that there was a pre-existing pathologic state plus a superimposed acute change. The pre-existing process consisted of (1) thickening and hyalinization of the media of the left coronary tree including the small branches with splitting and rupture of the elastic fibers, with and without deposits of lime salts, and (2) numerous small and large fibrotic scars of the myocardium, especially the left ventricle, and to a minor degree of the anterior part of the interventricular septum. The acute changes consisted of irregularly shaped hemorrhages of varying size located in the pericardium, the endocardium, and within the papillary muscles and the myocardium of the left ventricle. Most of these hemorrhages were fresh and no reaction was noticeable. There was, however, one area where the hemorrhage was beginning to be organized from the periphery.

The aorta showed heaping up of the intima with cholesterol depositions, with and without calcification. The adventitia showed extensive fresh hemorrhages.

In the kidneys, there were marked vascular changes in the glomeruli with hyalinization of the loops. Distension of the convoluted tubules with degeneration of the epithelium and increase in the interstitial tissue was present. The arteries as well as the arterioles showed evidence of hyalinization of the media with splitting of the elastic fibers.

In the pericentral areas of the liver the sinusoids were markedly engorged with red blood cells and the adjacent parenchymal cells were compressed and vacuolated. The periportal liver cells were normal.

In the pancreas the parenchymal cells were well preserved and in rare areas there was infiltration of red blood cells. In the capsule, however, there were many collections of red blood cells and numerous macrophages containing yellow pigment.

The sinusoidal spaces of the spleen were markedly engorged with red blood cells. Frequently, the splenic architecture was distorted by areas of hemorrhage.

Comment and Summary

A case is presented demonstrating fatal widespread hemorrhage resulting from the use of dicumarol at what is ordinarily considered a safe and desirable therapeutic level. Furthermore, this fatality occurred despite prior use of the drug in identical dosage over a period of seven months without serious complications. It therefore appears that, even with careful laboratory control over a prolonged period of

time, factors of unknown nature may come into play and cause a fatal outcome. In this case the factor which was believed to be contributory to the widespread hemorrhage was the presence of severe hypertensive and arteriosclerotic cardiovascular disease. While the mechanism of bleeding in dicumarol poisoning is unknown and while severe hypertensive and arteriosclerotic cardiovascular disease does not primarily manifest itself by bleeding, it is supposed that in some way the presence of severe hypertension and arteriosclerosis impairs the endothelial continuity of the vascular tree with resultant increased diapedesis when dicumarol is present. The risk attending the administration of dicumarol in such a case is therefore so great that it behooves the physician to weigh carefully the indications for its use, even when accurate control is assured.

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BOOK REVIEW

Aneurysmes Arteriels et Fistules Arterio-Veineuses. *René Leriche.* Paris, France, Masson et Cie, 1949. 314 pages, 26 figures. 900 francs.

This treatise by a great authority on the subject deals in part with the anatomy and pathogenesis, but mainly with the surgical treatment of aneurysms and arteriovenous fistulas. The author makes a definite distinction between methods and procedures of surgical treatment. Under the heading of methods, he includes the general principles of therapy, because he believes that a method may be devised before the procedures for carrying it out are developed, although sometimes the procedures come first. Under the heading of methods he lists diminution of the afferent blood stream in a fashion to induce saccular thrombosis, excision of the sac with or without restoration of the circulation, and obliterative aneurysmography.

As a result of a thorough knowledge of the literature on the subject, and of his own vast experience in the field, the author has formulated 14 rules for the treatment of these pathologic conditions which should be of great assistance and importance to those engaged in this branch of surgery. The first and most important rule is that the surgical treatment of an aneurysm in a limb should not be undertaken without previous arteriography to determine the exact location and shape of the sac, the number of openings and their locations, the size of the afferent channel, the nature of the circulation within the aneurysmal sac, and the arrangement of the extrinsic as well as intrinsic collateral vessels, the nature of the arterial wall above and below as well as in the sac. He draws attention to many errors in treatment that have been made because arteriography was omitted from the study. Of the remaining thirteen rules, the most important are blocking of the sympathetic nervous system and even gangliectomy; as complete hemostasis as possible during the surgical operation; the re-establishment of continuity of the principle vascular trunk in cases of aneurysm at bifurcations; and the reconstruction of the arterial tree by direct end-to-end suture, after excision, when the loss of continuity is not too great (3 to 4 cm.).

He gives full instructions about the desirable position of the limb after the excision and reconstruction of the arterial tree by venous graft, with or without a vitallium tube. He draws attention to certain special anatomic and bacteriologic conditions afforded by the antibiotics and anticoagulants which may make excision and reconstruction the method of choice. The author favors the modern procedures which have become possible as a result of the development of less fragile sutures, more knowledge of the structure of the aneurysm, the availability of sulfonamides, penicillin, and heparin.

The book is well written and well illustrated, insofar as anatomy (including radiography) is concerned, but lacks illustrations of surgical procedures which would have enhanced the value of the book.

HARRY GOLDBLATT

ABSTRACTS

AVITAMINOSIS

Spies, T. D., and Stone, R. E.: Hypotension Associated with Nutritive Failure. Proc. Soc. Exper. Biol. & Med. **72:** 368, (Nov.), 1949.

The authors found that persons with nutritive failure have a blood pressure which is usually below normal and which tends to rise slowly as the nutritive failure is corrected.

The effect of desoxycorticosterone acetate in such hypotensive patients was determined by administration of this substance daily in varying dosage. After the third day, the patients complained of tightness of the skin around the ankles. There was a prompt increase in blood pressure readings and in body weight, and when the drug was discontinued, the blood pressure readings promptly returned to normal.

While the findings are of general interest, the authors do not recommend the use of desoxycorticosterone acetate as a therapeutic agent for hypotension.

MINTZ

BACTERIAL ENDOCARDITIS

Cohen, S. M.: Massive Cerebral Hemorrhage following Heparin Therapy in Subacute Bacterial Endocarditis. Report of Two Cases with a Review of the Literature. J. Mt. Sinai Hosp. **16:** 214 (Nov.–Dec.), 1949.

Two cases of subacute bacterial endocarditis caused by *Streptococcus viridans* in patients with rheumatic valvulitis were treated with sulfapyridine and intravenous heparin, the latter being given in doses sufficient to maintain the blood coagulation time at one hour. On the third and fourth days of heparin therapy, the patients developed neurologic signs, with coma and death supervening a few hours later. Postmortem examination revealed massive intracerebral hemorrhage—multiple in one case—characterized microscopically by showing little tendency to organization, the blood remaining fluid.

The author reviews 12 other postmortem reports of cerebral hemorrhage following sulfapyridine and anticoagulants or heparin alone, and concludes that a previous area of encephalomalacia caused by emboli from the valves is a region of lowered resistance to the rupture of cerebral vessels, and that the massive hemorrhage which results is due to the decreased coagulation of the blood.

CORTELL

Wallach, R., and Pomerantz, N.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis. New England J. Med. **241:** 690 (Nov. 3), 1949.

The authors report an unusual case of subacute bacterial endocarditis successfully treated with streptomycin. They also review the literature on this phase of therapy. The causative organism, a bacteroid, is rare in endocarditis. A 53 year old waiter with a clinical diagnosis of subacute bacterial endocarditis manifested an unfavorable response to large doses of penicillin. On the forty-second day after hospital admission the blood culture taken on the thirty-second day was reported positive for bacteroids. Streptomycin, 4 Gm. daily in divided doses every three hours, was then started and continued for twenty-eight days. Three days later the clinical improvement was marked. No new petechiae appeared. After discharge, he was in excellent health and working.

The authors conclude that penicillin in the amounts used inhibited the growth of the organism but could not effect a cure.

BELLET

De Swiet, J.: Subacute Bacterial Endocarditis due to *Salmonella typhi-murium* Brit. M. J. No. 4637: 1155 (Nov. 19), 1949.

A fatal case of subacute bacterial endocarditis due to *Salmonella typhi-murium* occurred in a woman, aged 19, who failed to show clinical improvement from penicillin therapy. A favorable reduction in the febrile state was noted following the use of Chloramphenicol and, to a lesser degree, by streptomycin. In spite of treatment, the disease progressed unabated with progressive toxemia, weakness and the appearance of petechiae and a cardiac murmur, the latter soon becoming high pitched and musical. The progress of the disease in this patient, irrespective of temperature reduction, suggests that a much higher maintainance dosage is required at the onset of treatment than is employed in typhoid fever (i.e., 1.5 Gm. Chloramphenicol every three hours instead of every twelve hours) and that this

treatment should be continued for at least twenty-eight days.

TANDOWSKY

BLOOD COAGULATION

Abrahams, D. G., and Glynn, L. E.: Heparin Tolerance in Rheumatic Fever. Clin. Sc. **8**: 171, 1949.

Heparin tolerance tests were compared in 16 normal individuals with 27 active rheumatic fever patients; 27 patients with active tuberculosis constituted a second group of controls having elevated sedimentation rates. In active rheumatic fever there was an increased resistance to heparin activity; the maximal prolongation of clotting was less than normal and clotting time returned to normal faster than in normal controls. In 12 rheumatic patients the tolerance returned toward normal as the rheumatic activity subsided. The sedimentation rate did not always increase proportionately with the heparin tolerance. There was an increased tolerance to heparin in active tuberculosis, but less so than in rheumatic fever.

The mechanism of increased heparin tolerance in rheumatic fever is unknown. There may be a lowered renal threshold to heparin; there may be heparin storage in the reticulo-endothelial system as demonstrated in rabbits by Piper. The authors suggest an inactivation of heparin in the blood stream by protein binding; preliminary experiments showed an in vitro resistance to heparin in blood from patients with active rheumatic fever similar to the in vivo findings with the heparin tolerance test.

GOSFIELD

Portmann, F. A., and Holden, W. D.: Protamine (Salmine) Sulphate, Heparin, and Blood Coagulation. J. Clin. Investigation **28**: 1451 (Nov.), 1949.

The authors reinvestigated the action of protamine sulfate on the coagulation of blood and its use as antagonist to heparin in both in vitro and in vivo experiments. They found that protamine sulfate in intravenous doses up to 100 mg. had no effect upon the clotting time of whole blood in human subjects and also had no effect as a local hemostatic agent in dogs.

In the presence of serum or whole blood, the neutralization ratio of protamine to heparin was 18.1 and an excess of either caused prolongation of the coagulation time. The anticoagulant effect of protamine, in insufficient amounts to cause complete inactivation of fibrinogen in whole blood, is due to its interference with the conversion of prothrombin to thrombin, which is not apparent in the presence of an excess of thromboplastin. No antithromboplastic action of protamine sulfate was demonstrated, but protamine does neutralize the serum heparin cofactor.

BUTTERWORTH

CONGENITAL ANOMALIES

Charlier, R.: Observations of Circulatory Physiology in a Case of Isolated Ventricular Septal Defect. Rev. belge de path. et de méd. exp. **19**: 175, (March), 1949.

Catheterization of the right heart and of the pulmonary artery was performed in a case of isolated ventricular septal defect (Roger's disease). Information given by the gas analyses of the blood samples secured from right auricle, right ventricle and pulmonary artery was sufficient for the diagnosis since the oxygen content of right ventricular blood and of pulmonary artery blood exceeded that of right auricular blood by 3 volumes per cent. Calculations of the output of the heart showed that the blood flow of the pulmonary artery was twice as large as the blood flow of the aorta. The preponderant intracardiac shunt of blood was directed from left to right, and the volume of blood shunted through the ventricular septal defect was equal to the blood flow of the aorta. The coexistence of secondary blood currents flowing from the right ventricle into the left ventricle was proved by two findings: the oxygen saturation of the blood in the femoral artery was lower (92 per cent) than normal, and the effective pulmonary artery flow was 11.5 per cent below that of the systemic circulation. Pulmonary stenosis did not exist because the mean blood pressure was higher in the pulmonary artery than in the right ventricle; the absence of pulmonary stenosis was also proved by the fact that the pulmonary blood flow was 200 per cent of the systemic blood flow. The high pressure of the right ventricle and the presence of intracardiac currents from right to left indicated a less favorable prognosis than usual.

LUISADA

Limon, L. R., and Rubio A. V.: Diagnosis of Interauricular Septal Defects by Catheterization. Arch. Inst. Cardiol. de Mexico **19**: 545 (Aug. 31), 1949.

Twenty-five patients with auricular septal defects were studied by means of cardiac catheterization. In one of the cases, the pulmonary veins opened into the right auricle, while in another there was also a mild pulmonary stenosis. In 15 cases, the catheter was introduced into one or more pulmonary veins; in 3 other cases, only into the left auricle.

Comparison of the oxygen content of the caval with the right auricular blood is often sufficient for diagnosis. However, exception to this is possible because: (a) the volume of blood flowing in the two venae cavae is different; (b) a laminar flow in the inferior cava or some other cause prevents an effective mixture within the right auricle; (c) the shunt is from right to left; (d) the flow from the left auricle is scanty; or (e) there is more than one lesion. The only absolute proof of the existence of an auric-

ular shunt is obtained by passing the catheter into the left auricle through the septum. Three types of shunts were demonstrated; these were left to right, bilateral, and right to left (inverted).

LUISADA

Campbell, M.: Genetic and Environmental Factors in Congenital Heart Disease. Quart. J. Med. **28**: 379 (Oct.), 1949.

Two hundred fifty cyanotic, and 50 acyanotic children with congenital heart disease were investigated for the genetic and environmental factors in the etiology of their disease. With the exception of rubella occurring during the first trimester of pregnancy, no other environmental factors were significantly involved. Rubella appeared to be responsible for 4 (1.6 per cent) of the 250 cases with cyanosis. There was also mental retardation in one of these cases and congenital cataracts in 2 others.

The occurrence of congenital heart disease in more than one member of the family is rare. There was no conclusive evidence of congenital heart disease occurring more frequently in children of consanguinous marriages. The causes of congenital heart disease are chiefly genetic, the best evidence for a genetic factor being the occurrence of more congenital cardiac defects in siblings and distant relatives than could be expected by chance. The author feels that, because the risk is small that other children in the same family will develop congenital heart disease, it is proper to tell the mother that there is no risk of other children being born with this disorder.

MARGOLIES

Selzer, A., and Lewis, A. E.: The Occurrence of Chronic Cyanosis in Cases of Atrial Septal Defect. Am. J. M. Sc. **218**: 516 (Nov.), 1949.

Atrial septal defect has been classified as a late cyanotic lesion, one in which terminal cyanosis, due to a reversal of the direction of the intracardiac shunt, occurs when cardiac failure results in increasing pressure in the right atrium. The authors observed a 35 year old man who showed chronic cyanosis, polycythemia and clubbing of digits without congestive failure, and who at autopsy was found to have an uncomplicated atrial septal defect. A review of 180 proven cases of atrial septal defects, with or without concomitant mitral stenosis, reported in the literature showed that in 11 patients persistent and longstanding cyanosis not associated with cardiac failure was present. Pathologic findings in these cases did not differ from those in other, noncyanotic cases. Large defects involving most of the atrial septum were common among cyanotic cases but there was no apparent relationship between the size of the defect and the presence of cyanosis. With the clinical and pathologic evidence pointing to a large volume of blood being shunted from the left to the right auricle, the most likely cause of cyanosis appears to be a free mixing of blood in very large septal defects and/or anatomic conditions permitting a stream of venous blood from the great veins to enter the left auricle directly.

DURANT

Andrews, C. T.: Kartagener's Syndrome. Brit. M J. No. 4693: 1269 (Dec. 3), 1949.

The author reviews the incidence of bronchiectasis with complete transposition of the viscera and other congenital lesions, and reports a case of a 44 year old man with bronchiectasis and situs inversus totalis, congenital pulmonary cysts, poorly developed nasal antra and congenital deafness with absent mastoid cells. He feels that a congenital abnormality of the bronchiolar wall is responsible for the bronchiectasis seen in such cases.

TANDOWSKY

Vass, A., and Mack, J. K.: Anomalous Drainage of the Pulmonary Veins into the Coronary Sinus, Report of a Case. Am. J. Dis. Child. **78**: 906 (Dec.), 1949.

A white female child who was said to be normal at birth was observed to have a dusky hue at 6 weeks of age. There was a loud systolic murmur over the precordium which was transmitted to the right side of the chest. At the age of 10 months a diffuse thrill, most pronounced in the third intercostal space to the left of the sternum, was felt. X-ray examination revealed the heart to be large and globular. The cyanosis increased and dyspnea at rest became constant. Signs of right heart failure became evident with hepatomegaly and edema of the face, hands and ankles. The electrocardiogram revealed right axis deviation and a suggestion of hypertrophy of the right side of the heart. Death occurred at the age of 19 months. At autopsy there was found: drainage of the pulmonary veins into the coronary sinus, a patent foramen ovale, a bicuspid tricuspid valve, hypertrophy and dilatation of the right side of the heart, chronic passive hyperemia of the lungs and other organs, and terminal verrucous endocarditis of the tricuspid and mitral valves.

There are only 7 cases reported which show drainage of all the pulmonary veins into the coronary sinus. The right heart must transport a greater load of blood than the left heart. Therefore, there is hypertrophy of the right, and relative atrophy of the left heart. In all of the reported cases, the foramen ovale was open and in one case there was a patent ductus arteriosus. As the foramen ovale and the ductus arteriosus become smaller, the load on the right heart increases and cardiac decompensation occurs.

MARGOLIES

CONGESTIVE HEART FAILURE

Davies, C. E., and Mackinnon, J.: Neurological Effects of Oxygen in Chronic Cor Pulmonale. Lancet, No. 2: 883 (Nov. 12), 1949.

Contrary to the accepted belief that oxygen at pressures up to one atmosphere benefits those with heart failure due to chronic disease of the lungs, these investigators have demonstrated that this may produce untoward changes in the intracranial circulation of patients with chronic cor pulmonale. The change consisted of a sudden increase in cerebrospinal fluid pressure when oxygen was given in concentrations of 50 to 100 per cent; this was not observed in controls. This increased pressure resulted in myoclonic arm movements in one patient and in coma in another.

TANDOWSKY

Lavenne, F.: Contribution to the Study of Cor Pulmonale in Silicosis. Acta cardiol. **4:** 245, 1949.

Silicosis is a frequent cause of chronic cor pulmonale; from 10 to 50 per cent of the patients with silicosis die with congestive heart failure. Three new cases are described by the author. The electrocardiogram showed right axis deviation of both the P waves and the QRS complexes, while the T waves were inverted in Lead I. In the right precordial leads, the QRS complexes were M-shaped and the intrinsicoid deflection was delayed. In the left precordial leads, S was particularly large. According to the author, the roentgenologic signs of cor pulmonale appeared at an earlier stage than the electrocardiographic changes. Autopsy revealed severe hypertrophy and dilatation of both the right auricle and the right ventricle. In one case, functional tricuspid insufficiency was proved by autopsy.

LUISADA

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Mussafia, A., and Comberiati, L.: On Certain Cases of Myocardial Infarction with Delayed Appearance of the Electrocardiographic Picture. Cuore e circolaz. **33:** 198 (Aug.), 1949.

Seven cases of recent myocardial infarction with delayed appearance of the typical electrocardiographic signs are described. The electrical picture appeared only after a period of from fifteen to sixty days. This fact is explained by one of the two following possibilities; (a) the initial small infarction was not revealed by the electrocardiogram, and later became larger through secondary extension; or (b) the infarction was formed slowly on account of partially or temporarily efficient collateral circulation, or because of a slow occlusion. The authors point out the inadequacy of single electrocardiogram in the diagnosis of myocardial infarction.

LUISADA

Storch, S., Pordy, L., and Kolker, J.: The Master "2-Step" Exercise Test in the Differential Diagnosis Of Coronary Artery Disease. New York State J. Med. **49:** 2843 (Dec. 1), 1949.

The authors present the case history of a 60 year old white man in whom differential diagnosis had to distinguish duodenal ulcer, cerebral lesion, or coronary disease because of the history of sudden attacks of syncope associated with pressure over the lower portion of the chest or upper abdomen which radiated to the midback. The pressure was not related to effort. With a normal physical examination, a Master "2-step" test was performed, and a diagnosis of coronary artery sclerosis was made. Nine months later the patient developed a classic anginal syndrome and shortly thereafter suffered an acute coronary occlusion with infarction. The authors believe this case demonstrates the value of the Master "2-step" test in substantiating the diagnosis of coronary artery disease in a patient whose previous history may be quite misleading.

SIMON

Gardner, F. E., and White, P. D.: Coronary Occlusion and Myocardial Infarction Associated with Chronic Rheumatic Heart Disease. Ann. Int. Med. **31:** 1003 (Dec.), 1949.

In 6,000 consecutive autopsied cases there were 436 cases of rheumatic heart disease and 513 cases of coronary heart disease. Seven per cent of the cases with rheumatic heart disease had associated coronary artery disease and 6 per cent of the cases of coronary heart disease had associated rheumatic heart disease. There was no evidence to suggest that rheumatic heart disease has any influence on the development of coronary artery degeneration. The purpose of this paper is to emphasize the relative frequency of these two types of cardiovascular disease as coexistent entities. Awareness of this association by clinicians is not yet sufficiently prevalent

WENDKOS

Epstein, F. H., and Relman, A. S.: Transfusion Treatment of Shock due to Myocardial Infarction. New England J. Med. **241:** 889 (Dec. 8), 1949.

The authors studied the effect of whole blood transfusion in therapy of shock due to myocardial infarction. A systolic blood pressure of less than 90 in patients presenting the clinical picture of peripheral vascular collapse was taken as the criteria for shock. Blood was administered at a rate of 250 cc. per hour. The total amount of blood given averaged 750 cc. per patient. In all, 30 patients received transfusions and the results were compared with those in 20 cases who did not receive parenteral therapy.

The results showed a mortality rate of 90 per cent in the transfused group as compared with 85 per cent in the control series. Improvement in the shocklike state resulted in 37 per cent of those patients receiving blood, whereas the blood pressure rose in only 25 per cent of the control group. Cardiac failure was increased in 20 per cent of the transfused patients as contrasted with 15 per cent of the controls.

Since heart failure increased almost as often in

the control group as in those patients receiving blood the authors conclude that this mode of therapy is relatively safe. However, they did not feel that blood transfusion improved the mortality rate in patients with shock due to myocardial infarction.

NADLER

Douglas, A., and Marienberg, L.: Acute Myocardial Infarction in a Sixteen-Year Old Boy. New York State J. Med. **49:** 2845 (Dec. 1), 1949.

The authors report a case of acute myocardial infarction with recovery in a 16 year old boy. The clinical picture and the course were typical. The patient was very obese and the authors believe that the relationship of obesity to coronary sclerosis in the young is again demonstrated by this case.

SIMON

Hausamman, E.: Coronary Sclerosis in Older People as Compared to Coronary Sclerosis in the Young. Cardiologia **14:** 225, 1949.

The author examined the coronary arteries of 69 hearts obtained from routine autopsies on patients who died from various diseases. The age of the patients varied between 45 and 90 years (average 66.9). Twenty-eight of the patients were female. A pronounced degree of coronary sclerosis was found in 60 hearts. More numerous areas of necrosis with fatty degeneration and calcification were found in the intima of these patients than in those of patients in younger age groups, but no essential differences were seen in the arteriosclerotic process. Vacuolarization of the intima was observed in 59 cases. It was attributed to the formation of vascularized granulation tissue. Intramural hemorrhages, consequences of this vascularization, were seen in 11 vessels. In another 11 vessels, residual findings pointed to an old hemorrhage. In 3 cases, evidence of a fresh or old coronary thrombosis was found. In all 3 instances an intramural hemorrhage from an abnormal vessel in the intima was found to be responsible. In 5 out of 6 female patients who had gall stones, severe coronary sclerosis was found. In 3 cases with tuberculosis and 16 cases with rheumatic fever, coronary sclerosis was moderate.

SCHERF

Bean, W. B., Flamm, G. W., and Sapadin, A.: Hemiplegia Attending Acute Myocardial Infarction. Am. J. Med. **7:** 765 (Dec.), 1949.

The authors delineate a syndrome of acute focal cerebral disease occurring coincident with, or shortly after, acute myocardial infarction. Six case reports are presented.

The neurologic disability is commonly misdiagnosed as cerebral hemorrhage, embolus or thrombosis, but is the result of localized cerebral ischemia secondary to the shock resulting from the acute myocardial catastrophe. Pre-existing cerebral arteriosclerosis with diminution of blood flow may determine the area or areas of the brain most severely affected. If the shocklike state is of brief duration, capillary damage is slight and the focal neurologic disability may be of transient nature. If shock is of longer duration, continued capillary anoxia results in localized edema and tiny hemorrhages with irreversible cerebral changes. This syndrome of acute, secondary, focal cerebrovascular disease, not the result of embolism, thrombosis, or hemorrhage, may also complicate postural hypotension, shock, paroxysmal arrhythmias, and acute left ventricular failure. The disorder is to the brain what acute coronary insufficiency is to the heart.

HANNO

ELECTROCARDIOGRAPHY

Rasario, G. M.: On Partial Auricular Fibrillation. Riforma Med. **62:** 377 (July 31), 1948.

The author describes a case of rheumatic heart disease with mitral stenosis and insufficiency and an associated ventricular arrhythmia and auricular flutter. After digitalization, the ventricular rhythm became regular. Large P waves at the same rate as the ventricular complexes were revealed by the standard leads. On the other hand, special leads, more sensitive to the currents of the auricles, revealed that, in addition to the former, there were also smaller waves with a rate of 600 per minute. The author interprets this case as having a sinus rhythm in the right auricle with an impure flutter in the left.

LUISADA

Donzelot, E., Milanovich, J. B., and Plavsic, C.: Frontal and Horizontal Spatial Vectography in the Syndrome of Wolff, Parkinson and White. Arch. d. mal. du coeur **42:** 780, (Aug.), 1949.

On the basis of twenty-five observations, the authors came to the conclusion that the Delta wave, representing the electrical sign of the Wolff-Parkinson-White syndrome, develops most often in the direction of the initial part of the spatial vectogram. Thus, by establishing the position of the delayed part within the vector loop, the W-P-W syndrome can be distinguished from bundle branch block. However, the syndrome can be complicated by coexistence of bundle branch block, an example of which is presented. In this case the authors used an intravenous injection of atropin to revert the combined pattern of bundle branch block and W-P-W syndrome gradually into a pure pattern of left ventricular hypertrophy. Simultaneous registration of the carotid pulse demonstrated that the presence of a Delta wave, indicating pre-excitation of the right ventricle, did not affect the onset of the ejection of the left ventricle. A statistical evaluation of the 25 cases of W-P-W syndrome with respect to the electrical axis and the position of the heart, showed that an electrically horizontal heart was usually seen in cases with left ventricular hypertrophy, and

a semivertical or vertical position was present in clinically normal hearts.

PICK

Soulié, P., Laham, J., and Papanicolis, I.: An Electrocardiographic Study of the Parietal Aneurysms of the Cardiac Apex. Arch. d. mal. du coeur **42**: 569 (Sept.), 1949.

Fifteen cases of ventricular aneurysm are described, 7 of which were studied at necropsy. The authors conclude that severe right axis deviation (between plus 120 and minus 90 degrees) strongly favors the possibility of a parietal aneurysm of the apex. On the other hand, severe left axis deviation (between minus 70 and minus 90 degrees) also may indicate either aneurysm of the apex or extreme thinning of the apical wall. It is the authors' impression that large aneurysms or those of sudden development in a heart of normal size result in a right axis deviation; on the other hand, small aneurysms or those developing in hypertrophied hearts result in left axis deviation. Upward, persistent displacement of the S-T segment in the precordial leads is frequently encountered in apical aneurysms. The absence of electrocardiographic data does not exclude parietal aneurysms.

LUISADA

Deglaude, L., and Laubry, P.: Observations on Technique and Interpretation of the Esophageal Leads. Arch. d. mal. du coeur **42**: 861 (Sept.), 1949.

To obtain esophageal leads, the authors introduce a semirigid tube into the stomach, the curvature of the tube tending to follow in a forward direction the inferior surface of the heart. Normal tracings and tracings in cases of posterior infarction are discussed. The advantage of the use of the "gastric" lead for the study of posterior infarctions is emphasized.

LUISADA

Greenfield, I.: Electrocardiographic Changes in Malaria. New York State J. Med. **49**: 2339 (Dec. 1), 1949.

The author presents the case report of a 30 year old white man with recurrent vivax malaria who, while under atabrine therapy, experienced an episode of precordial lancinating pain, perspiration, and weakness. There was no significant drop in blood pressure. An electrocardiogram taken at this time revealed depression of the T waves in Leads I, II, CF_2, CF_4 and CF_5. The entire contour of the complex in Lead III had also changed. During this episode, malarial parasites were again present in the blood smear. With bed rest, the symptoms subsided and after six weeks the electrocardiogram returned to the control pattern. At no time was a pericordial friction rub heard.

Since the electrocardiographic changes were not reproduced following repeated administrations of atabrine in the absence of malaria, the author believes it reasonable to eliminate atabrine as the causative agent. In the absence of any other explanation for the symptomatology, he believes that it is reasonable to assume that the heart muscle changes resulted from malarial thrombi in the myocardium.

SIMON

Goldberger, E.: Effects of Clockwise Rotation of the Heart on the Electrocardiogram. Am. J. Med. **7**: 756 (Dec.), 1949.

The author describes changes in the precordial and unipolar extremity leads occurring in clockwise rotation of the heart. With marked clockwise rotation, Leads V_1 through V_5 or V_6 may face the epicardial surface of the right ventricle and show rS and RS patterns, and Lead aV_R may present a QR, Qr or qR configuration. When extreme clockwise rotation is present, a QR or qR pattern may also occur in Lead V_1 and sometimes in Lead V_2.

HANNO

First, S. R.: Electrocardiographic Evaluation of Boeck's Sarcoid and Advanced Pulmonary Tuberculosis: Special Reference to Interpretation of the Multiple Unipolar Leads. Am. J. Med. **7**: 760 (Dec.), 1949.

Electrocardiographic studies with multiple leads were performed on 7 cases of Boeck's sarcoid with pulmonary manifestations and on 20 cases of far advanced pulmonary tuberculosis. Changes indicative of left ventricular hypertrophy were noted in 6 of the former group and in none of the latter group. Involvement of the myocardium in sarcoidosis is offered as the explanation of the electrocardiographic changes, but the selective involvement of the left ventricle is unexplained. The author suggests that the electrocardiographic finding of left ventricular hypertrophy may help in the differentiation between pulmonary sarcoidosis and pulmonary tuberculosis.

HANNO

Guggenheim, M.: A-V Conduction Disturbances in Mother and Daughter. Cardiologia **14**: 251, 1949.

The author describes the case of a 50 year old woman with hypertension, anginal pain, and complete A-V heart block, complicated by Stokes-Adams attacks. The 15 year old daughter of this patient developed fainting spells following tonsillitis. A partial A-V block with a conduction time of 0.28 second was found in the electrocardiogram. The lesion in this case was attributed to myocarditis. An inherited inferiority of the conduction system was held responsible for the occurrence of A-V block in two generations with two different etiologies.

SCHERF

ENDOCRINE EFFECTS ON CIRCULATION

Knowlton, A. I., Loeb, E. N., Seegal, B. C., and Stoerk, H. C.: Desoxycorticosterone Acetate: Studies on the Reversibility of its Effect on Blood Pressure and Renal Damage in Rats. Endocrinology **45**: 435 (Oct.), 1949.

The authors demonstrated that rats in which nephritis was produced by the injection of a potent rabbit anti-rat kidney serum developed a moderate hypertension with and without dietary sodium chloride restriction. If desoxycorticosterone acetate (DCA) was given, the hypertension appeared more rapidly and reached a greater height. If the DCA was then withdrawn there was a decline in the blood pressure to the level of non-DCA treated rats. In these studies, DCA had no augmenting effect on the course of the severe nephritis, such as had been previously reported.

CORTELL

Dorfman, R. I.: Influence of Adrenal Cortical Steroids and Related Compounds on Sodium Metabolism. Proc. Soc. Exper. Biol. & Med. **72**: 395 (Nov.), 1949.

This paper is concerned with the study of various adrenal cortical steroids and related compounds on sodium metabolism. Desoxycorticosterone produced a significant sodium retention when amounts as low as 1 microgram were given. Desoxycorticosterone acetate produced sodium retention at a concentration of 25 micrograms. 4-pregnenol-21-trione-3, 12, 20, 21-acetate gave a significant retention at 1340 micrograms. 17-hydroxycorticosterone and 17-hydroxy-11-dehydrocorticosterone caused an immediate increase in sodium excretion during the first twenty-four hours but the sodium excretion returned to control levels in spite of continuous treatment. A group of other steroids studied were found to be inactive at the doses tested.

MINTZ

HYPERTENSION

Harland, J. C., and d'Abreu, F.: Lumbo-Dorsal Sympathectomy in Severe Hypertension. Brit. M. J. No. 4614: 1019 (June 11), 1949.

The author reports lumbo-dorsal sympathectomy performed on 24 patients with severe hypertension. Five patients had chronic renal disease and 19 were classified as having essential hypertension. Six patients of the last group were considered to have malignant hypertension.

Of the 24 cases, 4 patients died and 18 were studied after the operation. In only 5 of the 18 cases was the fall in blood pressure appreciable, but even in these the postoperative blood pressure level remained well above normal. Retinal edema, hemorrhages, and exudates disappeared except in one case. The cardiovascular state of 4 cases of hypertensive heart disease appeared to improve temporarily. Cardiac asthma disappeared, and breathlessness on exertion diminished in some. Four of the 6 patients with malignant hypertension died. The two who survived showed considerable improvement. One of the most impressive features of the operative results was the general improvement in health that resulted.

The authors conclude that in a properly selected case the relief is greater than that which can be obtained by medical treatment alone. The operation should be limited to severe and rapidly progressive cases which comply with the following conditions: the age should be less than 50 years, the renal function should be good, there should be no evidence of coronary or cerebral artery disease, and there should be no severe heart disease or heart failure. Operation in early and mild cases is not advised.

BELLET

Hughes-Jones, N. C., Pickering, G. W., Sanderson, P. H., Scarborough, H., and Vandenbroucke, J.: The Nature of the Action of Renin and Hypertensin on Renal Function in the Rabbit. J. Physiol. **109**: 288 (Sept. 15), 1949.

The purpose of this investigation was to determine whether hypertension has the same effect as renin on renal function in the rabbit. It was found that, qualitatively, both increase sodium and chloride excretion, increase urinary output, affect the inulin and diodone clearances in the same way, and produce a urine, the chloride content of which tends to approximate and slightly exceed that of plasma. On the basis of these results the authors conclude that the changes in the volume and composition of the urine during the diuresis produced by renin and hypertensin are due to suppression of the tubular capacity differentially to reabsorb water, sodium, and chloride. It was suggested that the effect of renin on the kidney was mediated by hypertensin.

ABRAMSON

Lampen, H., Kezdi, P., Koppermann, E., and Kaufmann, L.: Neurogenic Increase of Blood Pressure Produced Experimentally in Patients with Arterial Hypertension. Ztschr. f. Kreislaufforsch. **38**: 577 (Oct.), 1949.

In patients in older age groups with hypertension and in patients with essential hypertension and malignant hypertension, the functional state of the pressoreceptors was studied by means of bilateral blockade of the carotid sinus by Novocain. The patients referred to reacted to this procedure by a sudden increase of the pulse rate as well as of systolic and diastolic pressure readings. This was interpreted to indicate that a reflex regulation of the blood pressure is present in hypertension. Normotonic subjects reacted to the same procedure by showing a rise in pressure that was more marked but of shorter duration. The counter-regulation in

normotensive subjects by the remaining pressoreceptors was absent in the hypertensive patients, indicating that in the latter there is a higher threshold for impulses in the whole system due to the impaired elasticity throughout the vascular tree. A neurogenic mechanism in the production of hypertension is acceptable; however, hyposensitivity of the pressoreceptive system on an anatomical basis has to be postulated instead of a hypersensitivity, which has been assumed by others to be present in hypertension.

PICK

Bechgaard, P.: Electrocardiographic Investigation of 264 Cases of Hypertension. Brit. M. J. No. 4636: 1089 (Nov. 12), 1949.

In his review of 890 patients with hypertensive disease, the author reports that the prognosis is worse in those patients presenting an initial abnormal electrocardiogram. On the basis of T-wave changes, a group of 264 patients were studied over a period of eleven years. In those with definitely abnormal electrocardiograms little tendency was shown for improvement; in only 3 did the electrocardiogram improve. The mortality rate in men *with* electrocardiographic evidence of myocardial disease was five and one-half times greater, and for women three times greater than the average mortality, against two and one, respectively, for hypertensive subjects *without* electrocardiographic change. The author feels that any therapy for hypertension capable of effecting a regular and lasting improvement of the electrocardiogram should be of value.

TANDOWSKY

Wilkens, R. W., Stanton, J. R., and Freis, E. D.: Essential Hypertension, Therapeutic Trial of Veriloid, a New Extract of Veratrum Viride. Proc. Soc. Exper. Biol. & Med. **72:** 725 (Nov.), 1949.

Veriloid, a purified alkaloidal fraction of veratrum viride, was given to 10 hospitalized patients after a control period of at least forty-eight hours of bed rest. Measurements of arterial pressure and pulse rate were made at least three times a day and, when these had stabilized, every half hour for the two hours before and four hours after the administration of the drug.

Veriloid was also given to 25 ambulatory cases after three measurements were made of arterial pressure and pulse rate under standard conditions during each visit. The patients were then given 1 or, at the most, 2 mg. of Veriloid four times a day at intervals of at least four hours. The patients were gradually worked up to their nauseating dose, and then maintained at a slightly reduced dosage, which averaged 2 mg. of Veriloid four times a day at the end of three to four weeks. Patients were cautioned, if nauseated or otherwise uncomfortable, to remain recumbent and to reduce slightly their subsequent doses. On this regimen, severe collapse reactions were rare. The antidote used for these reactions was ephedrine sulfate (30 to 45 mg.) and/or atropine (0.5 to 1 mg.).

Both groups of patients had a definite drop in both systolic and diastolic pressures. The drug produced less nausea and vomiting than any other active oral preparation available and could be given for short periods or for periods as long as five months. Meticulous regulation of dosage is important in obtaining optimum results.

MINTZ

Drill, V. A.: Reactions from the Use of Benzodioxane (933 F) in Diagnosis of Pheochromocytoma. New England J. Med. **241:** 777 (Nov. 17), 1949.

The author discusses 2 patients with hypertension in whom the adrenolytic drug, benzodioxane (933 F), was used as a diagnostic aid to rule out pheochromocytoma. Each patient received an intravenous infusion of 5 per cent glucose. After about twenty minutes, 933 F was injected into the infusion tubing for two or three minutes in a dose of 10 mg. per square meter of surface area. Both patients showed a marked rise in the systolic and diastolic blood pressure and an increase in pulse rate. Nausea, headache, dizziness, flushing and precordial pain were experienced. The author concludes that the stimulation of the central nervous system caused by 933 F is a dangerous side reaction, and is an inherent property of such compounds that apparently becomes more manifest in patients with hypertension that is not due to pheochromocytomas.

NADLER

Bang, H. O., Bechgaard, P., Nielson, and A. Levin: Low-Salt Diet in Treatment of Hypertension and Hypertensive Heart Disease. Brit. M. J., No. 4638: 1203 (Nov. 26), 1949.

In a group of 26 patients placed on a low-salt diet, 23 presented a fall in blood pressure. The authors conclude that a diet of this type may produce a fall in blood pressure in many hypertonic subjects, but not in all. Addition of salt to these patients' diets without their knowledge caused a rise in blood pressure. No cause for this effect is offered, but they feel that investigation into plasma volume and renal function may offer the necessary clue. They warn of the danger in using a low-salt diet where extensive renal damage is demonstrable.

TANDOWSKY

Bradley, J. E., and Drake, M. E.: The Effect of Preoperative Roentgen-Ray Therapy on Arterial Hypertension in Embryoma (Kidney). J. Pediat. **35:** 710 (Dec.), 1949.

Ten patients with Wilms' tumor associated with hypertension were given preoperative roentgen-ray irradiation. Four patients had a marked fall in blood pressure five to eight days after the beginning of treatment. Three of these 4 patients had a detectable

reduction in size of the tumor, but this was preceded in all cases by the change in blood pressure. Two of the patients in this treated group were still alive after five and one-half and eight years, respectively, both with normal blood pressure. Six patients given preoperative irradiation did not respond with any lowering of blood pressure or reduction in the size of the tumor five to eight days after beginning treatment. One patient had a normal blood pressure following preoperative irradiation, which persisted following nephrectomy until six months later, when hypertension occurred with the development of pulmonary metastases. Irradiation to this area resulted in a return of the blood pressure to normal limits. Eleven and one-half months following the initial admission, this patient died with severe hypertension. Postmortem examination showed widespread pulmonary and hepatic metastases, but no evidence of tumor recurrence at the original site and with no involvement of the other kidney.

The cause of hypertension seen in Wilms' tumor remains unknown. While the preponderant majority of patients with renal embryoma have an associated hypertension, some do not. Although the concept of renal ischemia seems applicable to some of these cases, it does not seem to apply to the case where metastatic lesions in the lungs and in the liver were associated with a return of hypertension. In addition, repeated attempts have failed to demonstrate the presence of a pressor substance in these tumors.

SCHWARTZ

Stamler, J., Katz, L. N., and Rodbard, S.: Serial Renal Clearances in Dogs with Nephrogenic and Spontaneous Hypertension. J. Exper. Med. **90:** 511 (Dec.), 1949.

The authors compared serial renal clearances in dogs with spontaneous hypertension, in dogs rendered hypertensive by the Goldblatt method, and in normal dogs. Three dogs with spontaneous hypertension were found to have normal renal plasma flow and glomerular filtration rate. During the third year of their known hypertension, serial renal clearances done at intervals showed no tendency for the animals to develop impaired renal function. Pathologic studies on 2 of these dogs revealed slight to moderate chronic focal lesions in the kidneys, and bilateral adrenal cortical adenomatous hyperplasia.

Seven nephrogenic hypertensive (Goldblatt method) dogs were studied. Clearances revealed that some exhibited normal kidney function, while others showed depression of renal plasma flow and glomerular filtration rate. In the latter, the filtration fraction was elevated in some and not in others. Serial renal clearances showed no tendency toward progressive impairment of kidney function. This was found regardless of the duration of the hypertension and whether or not the immediate postoperative clearance values were normal or depressed. Kidney function was not found to improve over the course of a year or more in dogs submitted to the Goldblatt procedure, even though these dogs showed immediate depressed clearance postoperatively. Autopsies on 3 such dogs showed minimal renal changes in one, unilateral kidney atrophy with contralateral hypertrophy in 2 and normal adrenals in all.

In general, renal clearances showed correlation with postmortem kidney findings, although normal renal clearances occurred with anatomically abnormal kidneys. The present studies suggest that mechanisms other than elevated blood pressure operate to produce progressive kidney damage and impaired renal function. It is apparent that canine chronic benign hypertension does not result in progressively impaired renal function, in contrast to the situation in human essential hypertension.

SCHWARTZ

Ayman, D.: Critique of Reports of Surgical and Dietary Therapy in Hypertension. J.A.M.A. **141:** 974 (Dec. 3), 1949.

The author points out that, because of the intrinsic shortcomings and deficiencies of the investigative studies, the enthusiastically proclaimed beneficial effects of dietary and surgical treatment in hypertension, are, in many instances, more apparent than real. The pretreatment blood pressure determinations are taken over too short a period of time to constitute a proper control; moreover, the pretreatment readings are made at a time when the patient is in an unaccustomed environment and, in the case of contemplated surgery, is emotionally upset because of this realization. These factors tend toward artifically high pretherapy blood pressure levels. The post-treatment pressure determinations, on the other hand, are made in the comparative calm following reassurance offered by dietary therapy or the lack of apprehension when operation is a thing of the past. In many instances the post-therapy period of observation has been too brief for any definitive evaluation. In the case of dietary programs, the beneficial effects resulting from weight loss itself have not been controlled. Moreover, several of the articles advocating the rice diet in hypertension have included patients with acute or chronic nephritis and/or cardiac decompensation. These are the principal targets of the author, who believes, nonetheless, that dietary and surgical methods have a place in the therapy of hypertension, albeit a small one.

HANNO

Kappert, V. A.: Investigation Concerning the Action of the New Dehydrogenated Ergot Alkaloids Associated with Disturbances in the Peripheral Blood Flow in Hypertension. Part IV. The Treatment of Hypertension with the DH-Alkaloids. Helvet. med. acta. **16:** 128 (Suppl. 22), 1949.

Hydergine (CCK 179), the combination of the

three dehydrogenated ergot alkaloids of the dimethylpyruvic acid group, has been shown to be the most active and best tolerated of the drugs investigated in the treatment of various forms of high blood pressure, such as juvenile hypertension, high blood pressure with subjective symptoms in the absence of organic damage, hypertension with prominent cerebral, retinal, renal or myocardial (electrocardiographic changes, angina pectoris) damage, hypertension with hormonal disturbances or with peripheral vascular disorders. Hydergine has proved clearly superior to bromides, barbiturates, and purine derivatives in the treatment of hypertension. Objectively, its therapeutic action is manifested by a reduction of the systolic and the diastolic blood pressures, improvement of the alterations of the eye grounds caused by hypertension, improvement of the electrocardiogram and of the disturbed renal function. A favorable influence is also obtained on the subjective symptoms of hypertension such as headache, vertigo, tinnitus, fatigue, sleeplessness, blurred vision, scotoma, hot flushes, ataxia, tremor.

In mild cases oral treatment with gradually increasing doses usually suffices. Generally improvement is seen after twelve days of treatment and a full therapeutic effect after twenty to thirty days. The combined oral and parenteral treatment with Hydergine, however, is considerably more effective; improvement is evident in seven days and a full therapeutic response is observed in sixteen days. The combined treatment is especially recommended for severe cases. Either method, however, requires single or repeated courses of two to three months' treatment interrupted by intervals free of medication, or continuous treatment. Medication should not be abruptly discontinued but gradually reduced —in oral therapy by a daily reduction of one to two drops with each dose.

The following directions are of fundamental importance for the treatment with Hydergine: (1) Therapy must be carried out over a sufficiently long time; when the first symptoms of improvement are observed, dosage should be increased until the optimal effect is obtained. (2) A sudden interruption of treatment or any abrupt change of the dosage should be avoided. (3) Therapy must be adjusted to each individual. Symptoms of intolerance may manifest themselves by stimulation of counter-regulatory mechanisms following excessive doses of the DH-alkaloids or, spontaneously, in autonomic instability. Supervision and periodic control of the patients are, therefore, imperative.

AUTHORS

PATHOLOGIC PHYSIOLOGY

Lange, K., Weiner, D., and Gold, M. M. A.: Studies on the Mechanism of Cardiac Injury in Experimental Hypothermia. Ann. Int. Med. **31:** 989 (Dec.), 1949.

Rabbits suffering from slow or rapid lowering of body temperature show a reduction in heart rate directly proportional to the fall of body temperature. The P-R interval and the QRS complex are also roughly proportional in their prolongation to the fall in body temperature. The relative prolongation of electrical systole is not a linear function of body temperature; it becomes relatively more prolonged at lower body temperatures. The very marked changes in the S-T segment and the T wave under such conditions show individual differences in extent and localization. The changes in rate and conduction are exclusively the result of the direct effect of cold. The prolongation of electrical systole is partly the result of cold directly on the muscle fibers and partly the result of anoxia due to lowered oxygen dissociation. The T-wave changes are exclusively the result of anoxia. The anoxic nature of the S-T segment and the T-wave changes, as well as part of the prolongation of electrical systole, is proved by the fact that increasing the oxygen dissociation of the blood by acidification reverses them to normal. Increasing the amount of oxygen physically dissolved in the plasma also reverses these changes. Anoxemia does not play any role in the production of any of the changes seen in the heart with exposure to cold.

WENDKOS

Shumacker, H. B., Jr., and Stahl, N. M.: A Study of the Cardiac Frontal Area in Patients with Arteriovenous Fistulas. Surgery **26:** 928 (Dec.), 1949.

Definite evidence of enlargement of the heart was observed in about one-half of a series of 185 soldiers with traumatic arteriovenous fistulas. The degree of cardiac enlargement appeared to be related to the size of the fistula, the duration of its existence, and perhaps its distance from the heart. The incidence and degree of cardiac enlargement and the rapidity with which this occurred were less in those patients with fistulas above the level of the heart than in those in whom the lesions were located in the pelvis and lower extremities. Reduction in the size of the heart was observed following excision of the fistula.

ABRAMSON

Benchimol, A. B., and Dias Carneiro, R.: Cardiovascular Changes in Toxemia of Pregnancy. Arq. brasil. de cardiol. **2:** 397 (Dec.), 1949.

The cardiovascular effects of toxemia of pregnancy were analyzed on the basis of a clinical and electrocardiographic study of 14 patients. In 4 instances the toxemic state resulted in a serious circulatory condition which was the direct cause of death in one case. Two patients with pre-existing essential hypertension showed a marked aggravation of their condition, as shown by increased blood pressure levels and transient T-wave changes. Case 3 developed congestive heart failure in the immediate postpartal period; complete recovery resulted

in less than one month. Pulmonary embolism due to massive obstruction of the pulmonary capillaries was demonstrated at autopsy in Case 4. A number of cells from this lesion were considered to have been forced through the pulmonary circuit since they were found in the myocardial tissue. It is suggested that this may be a significant factor in cardiac involvement in certain cases of toxemia of pregnancy.

SCHLESINGER

PATHOLOGY

Piotti, A.: Cardiac Tumors. Cardiologia **14**: 130, 1949.

Twenty-three cases of carcinoma and 7 of sarcoma and metastases in the heart were studied. In only 2 patients was the diagnosis made before death. Signs of cardiac failure were found clinically in 12 cases. The primary tumor in 6 of the cases with carcinoma was in the bronchi. The left ventricle was more often involved than the right. Tachycardia was the most frequent finding. Gallop rhythm and a pericardial friction rub were occasionally found. The electrocardiographic changes included bundle-branch block, auricular fibrillation, A-V nodal rhythm and abnormal T waves.

SCHERF

Lenzi, F., and Lenzi, S.: Considerations on Pathology of the Auricles. Cardiologia **14**: 21 (6), 1949.

The electrocardiogram of the turtle was studied by means of direct leads before and after auricular damage caused by cauterization. Four clinical cases presenting abnormalities of the auricular waves are presented.

The authors conclude that auricular fibrillation is a final stage which occurs only after a series of transitory auricular disorders. In certain cases, the following stages can be observed: (1) increased conductivity within the left auricle; (2) rapid left auricular rate followed by flutter and then fibrillation; (3) flutter of the right auricle with fibrillation in the left; (4) total fibrillation of the auricles. According to the authors, the occurrence of normal P waves does not exclude either auricular dissociation or partial fibrillation. The latter is revealed only by special leads for the study of auricular disorders.

LUISADA

Loeffler, E.: Unusual Malformation of the Left Atrium: Pulmonary Sinus. Arch. Path. **48**: 371 (Nov.), 1949.

An unusual anomaly of the left atrium in which that chamber was subdivided by a membranous fold extending downward from the roof of the chamber is reported. This fold, or curtain, bulged anteriorly and had a free sickle-shaped border below, just above the atrioventricular opening. The posterior compartment received the pulmonary veins; the anterior compartment continued into a normally-shaped auricular appendage and a normal mitral orifice.

This malformation has been previously described as a "triatrial" heart. The author believes that the proper term should be "pulmonary sinus heart" because the embryologic defect is a faulty incorporation of the pulmonary vein into the posterior wall of the atrium. The defect apparently has no special clinical aspect; it conceivably could give signs resembling mital stenosis. This particular patient died at the age of 70 years from hypertensive cardiovascular disease, in which the atrial defect was incidental.

GOULEY

Fischel, E. E.: The Role of Allergy in the Pathogenesis of Rheumatic Fever. Am. J. Med. **7**: 772 (Dec.), 1949.

Although rheumatic fever follows in the wake of a preceding Group A hemolytic streptococcic infection, accumulated evidence points to the fact that the streptococcic infection per se is not alone the causative factor in the development of the rheumatic state. The possibility that an allergic reaction on the part of the host is pathogenetically involved is suggested by much experimental and clinical work. These studies are reviewed in this paper.

Rheumatic-like lesions have been produced in the experimental animal by the induction of allergic reactions either of the necrotizing Arthus type, characterized by the presence of circulating antibodies, or of the bacterial tissue-fixed-antibody type. Sensitization by the production of isoantibodies and autoantibodies have given equivocal results. These animal experiments must be interpreted with reservation because, in the absence of other than morphologic criteria, the specificity of the induced lesions is open to question. From the clinical point of view, it is pointed out that there is as yet no test for the detection of specific antibodies in rheumatic patients not found in other individuals recovering from streptococcal infections.

HANNO

PHARMACOLOGY

Horwitz, O., Montgomery, H., Longaker, E. D., and Saÿen, A.: Effects of Vasodilator Drugs and Other Procedures on Digital Cutaneous Blood Flow, Cardiac Output, Blood Pressure, Pulse Rate, Body Temperature, and Metabolic Rate. Am. J. M. Sc. **218**: 669 (Dec.), 1949.

Experiments were designed and performed for the purpose of testing the selectivity of certain vasodilator drugs and stimuli for the peripheral cutaneous circulation. Heat, alcohol, moderate doses of Priscol, and food caused selective vasodilatation of the skin of the fingers and toes in varying degrees. Methacholine chloride and tetraethylammonium

chloride caused widespread vasodilatation, unselective for the skin of the fingers and toes.

The vasodilator stimuli which were studied were classified with reference to their actions on peripheral cutaneous blood flow and elsewhere as follows: (a) Those increasing only the cutaneous circulation. Examples are heat, food, alcohol, and Priscol in moderate doses. These have wide margins of safety. Decreases in "splanchnic" blood flow may well play a supportive role in their action. (b) Those which increase peripheral cutaneous flow and dilate other vascular beds sufficiently to induce increased cardiac output, in order to maintain blood pressure. Examples are methacholine chloride and large doses of tetraethylammonium chloride. These have narrow margins of safety. (c) Those which fail to increase peripheral cutaneous blood flow either with or without significant changes in cardiac output and blood pressure. Examples are tetraethylammonium chloride in small doses and niacin.

DURANT

Friedman, M., Byers, S. O., Bine, R., Jr., and Bland, C.: Renal Excretion of Digitoxin in Man following Oral Administration. Proc. Soc. Exper. Biol. & Med. **72:** 468 (Nov.), 1949.

The embryonic duck heart preparation, which is sensitive to minute amounts of digitoxin when present in Tyrode's solution and human serum, was used for quantitative detection of digitoxin excreted in the urine of patients receiving the drug. Each of 5 subjects were given 1.2 mg. of digitoxin orally and each excreted greatly varying amounts of the drug in the urine. The results indicated that approximately 14 per cent of the amount of digitoxin administered orally to these subjects could be recovered in the urine collected the first three days after administration of the drug.

MINTZ

Gonzales Sabathié, L., and Robiolo, O. A.: Paroxysmal Tachycardia in Infants below One Year of Age. Rev. argent. de cardiol. **16:** 277 (Sept.–Oct.), 1949.

Eight cases of supraventricular paroxysmal tachycardia are reported, all in infants below 1 year of age. Two of the infants died, one of vascular collapse after the end of the attack and the other of congestive failure during an attack. In 2 cases, vagal stimulation terminated the attack. Oral quinidine was useful in several cases.

Clinical and electrocardiographic characteristics of the attack are given; they include a post-tachycardia syndrome. The term "prenatal" is suggested in place of "congenital" for instances in which the paroxysmal tachycardia is observed before delivery.

LUISADA

PHYSICAL SIGNS

Seganti, A., and Scaturro, A.: The Phonocardiogram of Ventricular Septal Defect. Cuore et circolaz. **33:** 65 (April), 1949.

The phonocardiographic tracings of 9 children with a clinical diagnosis of Roger's disease were studied. The authors found some typical features in the tracings of the cardiac murmurs. They began in early systole with very slight oscillations scarcely higher than the isophonic line and continued during the rest of systole with wide oscillations of increasing-decreasing height. The features of the typical cardiac murmur are attributed by the authors to the balance of pressures between left and right ventricle in the various phases of systole.

LUISADA

Caló, A.: The Fifth Heart Sound. Cuore e circolaz. **33:** 208, (Aug.), 1949.

The author describes the phonocardiograms of 2 normal individuals and presents a new phenomenon, as yet undescribed in man: a reduplication of the third sound. The name "fifth sound" is suggested. The splitting or reduplication of the third sound had been described in animals by Luisada and Mautner, who attributed it to asynchronous rapid filling of the ventricles. The author, on the other hand, explains the fifth sound as a secondary vibration, due to an elastic reaction of the ventricular walls.

LUISADA

Gonzales Videla, J.: Inspiratory Reduplication of the Second Sound over the Aortic Area. Rev. argent. de cardiol. **16:** 306 (Sept.–Oct.), 1949.

Several cases presenting an inspiratory splitting of the second sound over the aortic area are described. They include cases of congenital dextrocardia, displacement of the heart toward the right, and traction on the vascular peduncle by adhesions. According to the author, observation of a split second sound at the right of the sternum should lead to suspicion of displacement, rotation, or inversion of either the heart or the large arterial trunks.

LUISADA

Froment, R., Gallavardin, L., and Cahen, P.: Clicks and Vibrations Caused by Constrictive Pericarditis. Arch. d. mal. du coeur **42:** 923 (Sept.), 1949.

A case of calcified pericarditis with a quadruple rhythm is described. A phonocardiogram revealed both an early systolic and an early diastolic snap. The systolic snap is more typical; the authors attribute it to vibration of either the calcified surface or the junction of articulated plaques. The diastolic vibration is less typical and can be found also in constrictive pericarditis without calcification.

LUISADA

Miller, J. H., and Wedum, B. G.: Cardiac Enlargement in Uncomplicated Mitral Insufficiency in Children. Am. J. Dis. Child. **78:** 703 (Nov.), 1949.

The authors report their observations on 82 children with a diagnosis of mitral insufficiency as the only rheumatic lesion. The diagnosis of mitral insufficiency was made in the presence of a long, blowing systolic murmur, varying in intensity from faint to loud, heard at the apex and transmitted into the axilla. All children were carefully examined by fluoroscopy and 24 per cent showed enlargement of the left ventricle. For controls, there were included 179 children with potential rheumatic heart disease, and 556 normal children with no heart disease. Four hundred and twenty-two (76 per cent) or the normal children had a functional systolic murmur. Of those with potential rheumatic heart disease, 1.6 per cent showed enlargement of the left ventricle.

The results of this study indicate that cardiac enlargement visible on fluoroscopy occurs in children with a diagnosis of mitral insufficiency based on the presence of a characteristic murmur, but that such enlargement is by no means the rule.

BELLET

PHYSIOLOGY

Schlapp, W., and Walker, A. G.: The Timing of Certain Circulatory Events in Man. J. Physiol. **108:** 458 (June 15), 1949.

The authors devised a technic in which the R wave of the electrocardiogram is used to "trigger" the sweep of a recording cathode-ray tube. By this method, the timing of the Korotokow blood pressure sounds showed a respiratory variation. Younger subjects showed more alterations, which were due to the shape of the pulse wave and to differences in its conduction velocity, than did older subjects. These variations were related to respiratory changes in blood pressure; in the case studied, the blood pressure was highest at expiration. At this time, there was maximal velocity of pulse wave conduction. The interval between the R wave and the first heart sound was found to be constant, while the interval between the R wave and the second sound varied with respiration. The second sound occurred later at expiration when the pressure was higher. Timing of the pulse wave also revealed that respiratory variations occurred; at expiration the pulse wave arrived earlier. Spontaneous changes in pulse wave velocity were noted during voluntary apnea, suggesting that these are dependent on blood pressure changes.

WAIFE

Barcroft, H., and Dornhorst, A. C.: The Blood Flow through the Human Calf during Rhythmic Exercise. J. Physiol. **109:** 402 (Sept. 15), 1949.

Using the venous occlusion plethysmographic method, the authors were able to study the rate of blood flow in the human leg during rhythmic contraction of the gastrocnemius muscle. Their results confirmed the findings of others that during the period of effort the mechanical hindrance of the contractions reduced the flow to 40 per cent of what it would otherwise have been.

ABRAMSON

Glaser, E. M.: The Effects of Cooling and Warming on the Vital Capacity, Forearm and Hand Volume, and Skin Temperature of Man. J. Physiol. **109:** 421 (Sept. 15), 1949.

Although it is generally accepted that cooling of the body reduces the peripheral blood flow, the question of where the blood is to be found when the peripheral blood vessels are constricted has not been satisfactorily answered. The authors investigated the problem through a study of vital capacity measurements in male subjects. Cooling the body produced a fall of vital capacity, while warming caused a rise in this measurement. This was interpreted to indicate that cooling results in movements of blood from the extremities to the lungs, while warming causes movement in the opposite direction.

ABRAMSON

Neil, E., and Redwood, C. R. M.: Blood-Pressure Responses to Electrical Stimulation of the Carotid Sinus Nerve in Dogs and Rabbits. J. Physiol. **109:** 281 (Sept. 15), 1949.

The effect of electrical stimulation of the carotid sinus nerve was studied in dogs and rabbits under chloralose anesthesia. Unlike the findings observed in cats, a marked depression of arterial blood pressure occurred. Normally, activation of the chemoceptors in the carotid sinus by changes in blood composition causes a rise in blood pressure, while excitation of the baroceptor mechanism by increasing the intrasinusal pressures produces a marked drop in pressure. The results obtained in the dog and rabbit through stimulation of the carotid sinus nerve, containing both types of fibers, were therefore interpreted to indicate that in these species the effects of baroreceptor fiber stimulation are predominant over those of chemoceptor fiber stimulation.

ABRAMSON

Orias, O.: The Genesis of Heart Sounds. New England J. Med. **241:** 763 (Nov. 17), 1949.

The author states that there is experimental and clinical evidence that the following events produce vibrations contributing to the formation of the first heart sound: muscular contraction and tension of the ventricular walls at the onset of ventricular systole (muscular factor); closure of the auriculoventricular valves (valvular factor); movements and distention caused by the ejection of blood from the ventricles into the arteries (vascular factor); and residual vibrations due to the preceding auricular contraction (auricular factor). The valvular factor

is the most important. The second heart sound is attributed to vibrations produced by closure of the semilunar valves and vibrations in the walls of the arteries and blood column. The third heart sound is due to vibrations of the ventricular wall produced by the inflow of blood from both auricles. Muscular contraction and distention, passage of blood through the auriculoventricular orifices, distention of ventricular walls by the inrush of blood from the auricles and friction of the auricle against neighboring structures are the underlying factors accounting for the auricular sound.

NADLER

Bruce, R. A., Lovejoy, F. W., Jr., Pearson, R., Yu, P. J. G., Brothers, G. B., and Velasquez, T.: Normal Respiratory and Circulatory Pathways of Adaptation in Exercise. J. Clin. Investigation **28**: 1423 (Nov.), 1949.

Thirty-five normal adults were tested at rest and after mild exercise. The blood pressure, arterial oxygen saturation, precordial electrocardiogram ventilation volume, expired gases and respiratory rate were measured by means of continuous recording apparatus while the subject was walking on a treadmill. The authors' results confirmed previously reported changes in gas composition and showed that adaptive changes in respiration and circulation complement and spare each other by differences in time and rate of change of the various cardiac and pulmonary functions.

BUTTERWORTH

Kelly, H. G., and Bayless, R. I. S.: Influence of Heart Rate on Cardiac Output. Lancet No. 2: 1071, (Dec. 10), 1949.

The authors report a study of the effect of digitalis on heart rate and cardiac output in the presence of auricular fibrillation and sinus rhythm. They investigated this relationship by determining the right auricular pressure and oxygen saturation of venous and arterial blood by the use of cardiac catheterization in subjects with and without cardiac failure. Digoxin was instilled intracardially (0.75 to 1.5 mg.) in 27 patients, 12 with sinus rhythm and 15 with auricular fibrillation. The effect of atropine was similarly studied in 20 patients.

Following Digoxin injection in the presence of cardiac failure, the rise in cardiac output was as pronounced in those with sinus rhythm as in those with auricular fibrillation. The authors found no relationship between the degree of slowing and the increase in cardiac output. Relief of venous congestion occurred independently of the degree of slowing. Cardiac output improved whether the ventricular rate was slow or fast. Atropine in normal and failing hearts produced a fall of auricular pressure and a rise in cardiac output. There was no evidence that acceleration of rate produced by atropine either depressed cardiac output or increased venous congestion. Following Digoxin injection, the use of atropine in fibrillating hearts reversed the slowing effect without counteracting either the rise in cardiac output or the fall in venous pressure caused by Digoxin. The same held true for patients with sinus rhythm.

TANDOWSKY

Bucht, H.: Examination of the Renal Plasma Flow by Means of Para-Amino-Hippuric Acid (PAH) Using one Intramuscular Injection. Scandinav. J. Clin. & Lab. Investigation **1**: 126 (No. 2), 1949.

The author describes a technic for the examination of renal plasma flow, using paraaminohippuric acid given in a single intramuscular injection together with a local anesthetic and adrenalin. Use of the local anesthetic avoided the pain which ordinarily followed the intramuscular injection of concentrated PAH. The injection of a small amount of adrenalin prevented a too rapid fall in plasma concentration of PAH without influencing the blood pressure or pulse rate. The most favorable mixture was found to consist of 0.3 ml. of 20 per cent PAH and 0.05 ml. of 2 per cent xylocain-exadrin (containing 0.0006 mg. of adrenalin) per Kg. of body weight. Comparison of this method with the continuous intravenous technic of determining PAH clearance showed close conformity of the two methods.

SCHWARTZ

Lagerlof, H., Werko, L., Bucht, H., and Holmgren, A.: Separate Determination of the Blood Volume of the Right and Left Heart and the Lungs in Man with the Aid of the Dye Injection Method. Scandinav. J. Clin. & Lab. Investigation **1**: 114 (No. 2), 1949.

The authors describe a dye injection method for determining the blood volumes in the right and left heart and in the lungs in normal individuals and in patients with various types of heart disease. The blood volume between pulmonary artery and brachial artery was determined from the dilution curve of Evans blue dye injected into the catheterized pulmonary artery. The amount of blood in the systemic arterial system proximal to the point in the brachial artery where blood samples were obtained was calculated by multiplying the cross-sectional area of the aorta, determined roentgenologically, by the distance from the root of the aorta to the site of arterial puncture. This method of calculation was found to be reasonably accurate when compared with a direct determination in a case of auricular septal defect.

The blood volume of the right heart was determined directly by subtracting the volume found when dye was injected into the pulmonary artery by catheterization from that found after injection into the superior vena cava. Total blood volume

of the heart was calculated from the roentgenologic heart volume based on the known correlation between roentgenologic heart volume during life and heart weight at autopsy. The blood volume of the left heart was presumed to be half of the total blood volume of the heart.

The amount of blood in the pulmonary artery, capillaries and veins was calculated by subtracting the blood volume in the left heart and proximal part of the arteries from the blood volume found between pulmonary artery and brachial artery. No consistent change in pulmonary blood volume was found in patients with various degrees of decompensation, with mitral valvular disease or with hypertension.

SCHWARTZ

RHEUMATIC FEVER

Swift, H.: The Etiology of Rheumatic Fever. Ann. Int. Med. **31**: 715 (Nov.), 1949.

The groundwork for bacteriologic and immunologic studies in rheumatic fever was laid after the separation of Group A streptococci into various serologic types. The discovery of the method of separation led to immunologic studies of the antigenic components of these streptococci in rheumatic fever patients. This knowledge, in turn, provided the basis for various investigations of experimental streptococcal infections in rabbits. Eventually, by imposing on these animals infectious conditions approximately similar to those observed among rheumatic fever patients, a histopathologic picture closely resembling that of human rheumatic carditis was induced in their hearts. The small proportion of infected rabbits showing this picture roughly approximated the relative frequency of rheumatic fever encountered among patients infected with Group A streptococci. On the basis of these investigations and of the hypothesis employed in planning them, there seems to be furnished additional support to the theory that Group A streptococci are important factors in the pathogenesis of rheumatic fever. The investigations also indicate how these microorganisms may act in giving rise to this disease.

WENDKOS

ROENTGENOLOGY

W. H. Thompson, M. M. Figley, and F. J. Hodges: Full Cycle Angiocardiography. Radiology **53**: 729 (Nov.), 1949.

The authors present a method of automatic multiple rapid exposures in angiocardiography. Only two exposures per second could be accomplished with the existing apparatus but the authors expect to achieve five exposures per second soon.

The desirability of showing the complete cycle of circulation is illustrated in a case of aortic coarctation in which the filling of the right chambers, the pulmonary arteries and veins, the left chambers and the aorta and its main branches were well demonstrated. Three views of the right ventricle indicated the magnitude of changes in chamber size during systole. Multiple exposures in a patient with atrial septal defect showed such narrowing of the right ventricular outflow tract in one exposure that infundibular stenosis could well have been inferred were it not for the subsequent observation in which the expansion of this portion indicated that such an organic defect did not in fact exist. Still another series demonstrated increase and decrease in the diameter of a pulsating pulmonary artery.

The authors stress that integration of multiple serial angiocardiography with electrocardiography should provide us with more information on the sequence of events in the cardiac cycle than is available at present.

SCHWEDEL

Steinberg, I., Dotter, C., Peabody, G., Reader, G., Heimoff, L., and Webster, B.: The Angiocardiographic Diagnosis of Syphilitic Aortitis. Am. J. Roentgenol. **62**: 655 (Nov.), 1949.

The authors emphasize that the portion of the aorta most commonly affected in syphilis is the lower ascending portion, hidden by the heart in conventional roentgenograms but seen in the angiocardiogram. Measurements were made of aortic diameters in the mid-ascending, transverse, mid-descending and diaphragmatic portions in 100 normal subjects and in 60 patients in whom the diagnosis of syphilitic aortitis was entertained. Diameters were greatest in the ascending portion, diminishing progressively distally. In the normal mid-ascending aorta the range was 16 to 38 mm., and diameters over 38 mm. were considered abnormal. The diameters in all syphilitic patients exceeded the normal width, measuring 38 to 70 mm. (average 45.4 mm.). Other angiocardiographic findings were irregularity of the aortic lumen (95 per cent), calcification of the ascending aorta (26.6 per cent), aneurysm (41 per cent), abnormal thickness of the aortic wall, and tortuosity of the thoracic aorta.

The authors stress that aortic dilatation to a width exceeding 38 mm. could occur also with hypertension, rheumatic aortic valvular insufficiency and coarctation of the aorta. They did not observe aortic dilatation with arteriosclerosis alone.

SCHWEDEL

Healey, R. F., Dow, J. W., Sosman, M. C., and Dexter, L.: The Relationship of the Roentgenographic Appearance of the Pulmonary Artery to Pulmonary Hemodynamics. Am. J. Roentgenol. **62**: 777 (Dec.), 1949.

The authors analyzed pulmonary artery width (prominence) and amplitude of pulsations in relation to pulmonary artery flows and pressures measured by the method of cardiac catheterization. They concluded that flows of less than 7 liters per minute per square meter of body surface rarely produce

dilatation, whereas flows in excess of 7 liters usually do produce dilatation roughly proportional to the increase in flow. With increased flow there is a corresponding increase in the amplitude of pulmonary artery pulsations, noted either in the main pulmonary artery, its hilar branches, or both. Increase in pulmonary artery pressure also may cause dilatation and increased pulsations. The combination of increased flow and pressure is more likely to produce dilatation and increased amplitude of pulsations than either alone.

In pulmonic stenosis with normal or reduced flow to the lungs, the size and the pulsations of the pulmonary artery and its branches are normal or diminished; where there is post-stenotic dilatation this is confined to the main pulmonary artery, and does not extend to its branches. Normal pulmonary artery contours may be observed with atrial and ventricular septal defects, patent ductus arteriosus, Eisenmenger's complex, mitral stenosis and in pulmonary vascular disease. Such contours may be normal even when pulmonary artery pressures are moderately increased.

SCHWEDEL

Carrol, D. S., and Evans, J. W.: Roentgen Findings in Sickle-Cell Anemia. Radiology **53:** 834 (Dec.), 1949.

The authors describe the roentgenographic findings in 49 cases of sickle cell anemia of prolonged duration. The usual red blood count was less than three million. The chest findings indicated that cardiac enlargement is one of the most constant features of this disease, though the degree of enlargement varies considerably. The heart contour was globular, there was prominence in the pulmonary conus region and enlargement to the right and to the left.

Eleven of the 49 patients had clinical evidence of cardiac insufficiency, 2 with roentgenographic manifestations of pulmonary edema. The authors attributed the pulmonary findings in these 2 cases to sickle cell crises rather than to left ventricular insufficiency. In general, there was poor correlation between the presence and severity of roentgenographic findings and the severity or duration of the anemia. The presence of bone and joint pains, fever, leukocytosis, murmurs and cardiac enlargement also was suggestive of rheumatic cardiac involvement.

SCHWEDEL

Thoyer-Rozat, P., and Pirquet, J.: Angiocardiography. Clinical and Radiological Studies. J. de radiol. et d'électrol. **30:** 3 (1–2), 1949.

The authors cite their experience with 40 angiocardiographic visualizations. Patients were prepared by sedation, including morphine. Eight to 30 cc. of the opaque injectable substance were used in infants, and from 40 to 45 cc. in adults. The injection time was from 1.8 to 2 seconds. Ether and saccharine were used for circulation times. Their contraindications were severe allergy, anaphylaxis, nephritis, severe liver damage and coronary artery disease. Illustrations and diagrams of the circulation in various conditions are shown.

SCHWEDEL

Scott, W. G., and Moore, S.: Rapid Automatic Serialization of X-Ray Exposures by the Radiograph, Utilizing Roll Film Nine and One-Half Inches Wide. Radiology **53:** 846 (Dec.), 1949.

The authors describe the technical development of their apparatus for the taking of rapid automatic serial exposures on films measuring 9½ by 9½ inches. The entire process is automatic and continuous until the exposure button is released. Two films may be taken each second for as many as 40 exposures. Roll film is used and exposures are synchronized with a self-cocking Potter-Bucky grid. Usually exposures are 500 m.a., 1/20 sec., 65-100 K.V.P.

SCHWEDEL

Husebye, O. W.: Calcified Ductus Botalli Persistens. Acta radiol. **32:** 173 (30: IX), 1949.

The author describes the roentgenologic findings in a 60 year old man with a machinery murmur clinically diagnosed as patent ductus arteriosus. A double linear calcification was noted in the region of the ductus extending from the pulmonary artery to the aortic downward projection so frequently seen in this condition. This calcification was even better demonstrated by the technic of planigraphy. There was no operation or postmortem confirmation. Calcification of the patent ductus obviously is a contraindication to operation on this structure.

SCHWEDEL

Minot, G.: A New Method of Radiological Investigation: Radio-Electrokymography. J. de radiol. et d'électrol., **30:** 211 (3–4), 1949.

The author describes the development of electrokymography since the photoelectric cell was first used for this purpose in 1939. The present day machines and methods are described. Typical curves are shown of the left ventricle, right ventricle, left and right auricles, and the aorta. These are taken simultaneously with the electrocardiogram.

SCHWEDEL

Andersson, T.: Electrokymographic Recording of Auricular Movements. Acta Radiol. **32:** 121, (30: IX), 1949.

The author discusses the various sites at which auricular pulsations may be recorded with electrokymography and concludes that the best region for such recording is in the posterio-anterior projection, at the junction of the pulmonary arterial and left ventricular pulsations. Here, pulsations of the left auricular appendage could be elicited in 45 out of 50 cases, even though no definite auricular contour or pulsations could be recognized in this region. In

the other 5 cases transmitted pulsations from the left ventricle or pulmonary artery obscured the smaller auricular waves. The electrocardiogram and carotid artery pulsations were used as reference points for the identification of individual auricular waves.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Brock, R. C.: The Surgery of Pulmonary Stenosis. Brit. M. J. No. 4624: 399 (Aug. 20), 1949.

The author discusses the Blalock-Taussig postulate and upon this and the careful use of radiography, radioscopy, cardiac catheterization and angiocardiography, determines the extent and type of surgical intervention indicated. Various surgical technics and methods are reviewed. Because of the difficulty of vascular dissection and the inability to properly visualize the heart and origin of the pulmonary artery and aorta, the author feels that a right-sided approach to the stenotic valve is dangerous. The mortality rate of patients having the Blalock and Potts operation at the Guy's hospital was 15.5 per cent, which is similar to the results of Blalock. Fifty-six per cent of those who recovered presented almost perfect results.

The author feels that in the presence of pure pulmonary stenosis valvulotomy is the procedure of choice. He warns that heart failure may be expected during the course of this procedure, and early preparation must be made for cardiac revival immediately following the valvulotomy. The difficulty of correcting an infundibular stenosis, a complete atresia, and stenosis associated with Fallot's tetralogy is discussed; the author feels that valvulotomy should be the procedure of choice in these lesions. To date, he reports 5 successful cases in this group following this procedure.

TANDOWSKY

Swan, H. M. D., Maresh, G. J., and Fisher, G. R.: Criteria of Operability in Tricuspid Stenosis. J. Pediat. **35**: 604 (Nov.), 1949.

The basic pattern of congenital tricuspid stenosis consists of a diminutive or absent right ventricle with atresia or hypoplasia of both the pulmonary artery and the tricuspid valve. In order to be compatible with life, this lesion must be associated with an interauricular septal defect. A ventricular septal defect, or a patent ductus arteriosus, or both must be present also in order that blood may enter the pulmonary artery. Two cases are presented which illustrate the two ways in which blood may reach the lung, one by way of the patent ductus and the other by way of an interventricular septal defect and a hypoplastic pulmonary artery. The latter anomaly resulted in a diminished pulmonary blood flow at low pressure. The former anomaly resulted in a vigorous pulmonary blood flow at high pressure.

It is suggested that a method for differentiating these variants of the basic pattern of tricuspid stenosis is the response of the blood oxygen saturation to inhalation of pure oxygen. In patients whose lungs are supplied through a hypoplastic pulmonary artery, a marked shift in oxygen saturation of arterial blood upon inhalation of oxygen should not occur. For these patients an aortic-pulmonary shunt is indicated. In patients whose lungs are supplied through a large patent ductus with blood under high pressure and in whom vascular pulmonary changes have ensued, a marked shift in the oxygen saturation of arterial blood upon inhalation of oxygen may be expected. In these patients, operation is not indicated.

LECKS

Johnson, J., Kirby, C. K., Greifenstein, F. E., and Castillo, A.: The Experimental and Clinical Use of Vein Grafts to Replace Defects of Large Arteries. Surgery **26**: 945 (Dec.), 1949.

In an attempt to evaluate the use of vein grafts to replace arterial defects, the authors excised a segment of abdominal aorta in 17 dogs and obtained continuity of lumen by using a vena caval graft. In all instances the diameter of the vein graft was greater than that of the abdominal aorta. Although some dilatation of the grafts occurred, in none was there evidence of aneurysm formation. Progressive thickening of the vein was noticed, but the wall did not resemble that of an artery. The grafts appeared to function well and no changes in circulatory dynamics as reflected in femoral artery pulse pressure tracings were noted.

Because of the successful outcome in animals, superficial femoral vein grafts were used in 2 patients suffering from the tetralogy of Fallot to bridge a defect between the subclavian and pulmonary arteries. In one an excellent functional result was obtained while the other died postoperatively from pulmonary embolism.

ABRAMSON

Thomson, S. A., and Raisbeck, M. J.: The Surgical Rehabilitation of the Coronary Cripple. Ann. Int. Med. **31**: 1010 (Dec.), 1949.

This paper is concerned with an evaluation of the benefits to be derived from the introduction of talc powder into the pericardial cavity for the purpose of inducing a hyperemia of the myocardium and the stimulation of new intercoronary communications in patients suffering from coronary artery disease with disabling coronary insufficiency. Presumably, the adhesive pericarditis thus produced does not interfere with cardiac function nor does it increase cardiac work.

The procedure was employed in 36 patients with angina pectoris, all of whom suffered from an extreme degree of disability and failed to show any improvement after a prolonged period of medical treatment. Six patients died in the hospital after

operation, giving a hospital mortality of 16 per cent. Three of these patients died within forty-eight hours of coronary occlusion. The other 3 patients died within two or three weeks after the operation, 2 from a coronary occlusion which developed after the operation and one from a rupture through an unhealed infarct which was discovered at the time of the operation. From the standpoint of relief of the anginal pain, 70 per cent were markedly improved and another 15 per cent were moderately improved. According to their own estimate, 85 per cent of the patients were more than 50 per cent improved. Eight patients considered themselves to be completely relieved and normal. The ability to care for their daily needs has been restored to all the patients who are living. With only one exception, these patients have been able to return to their former occupations or to engage in other gainful occupations even though many of them had been completely incapacitated before the operation.

WENDKOS

THROMBOEMBOLIC PHENOMENA

Allen, A. W.: The Present Evaluation of the Prophylaxis and Treatment of Venous Thrombosis and Pulmonary Embolism. Surgery **26**: 1 (July), 1949.

The ratio of deaths from venous thrombosis and pulmonary embolism at present is still as great as existed ten years ago. In an attempt to elucidate the problem further, the author studied the clinical history of 2,929 patients receiving specific preventive or therapeutic measures for venous thrombosis. In 1,332 cases, bilateral superficial femoral vein interruption was performed for the treatment of thrombosis and of this number 6 succumbed to further emboli. In 950 patients falling into the older age groups, prophylactic superficial femoral vein interruption was performed, and of these, 4 died from pulmonary embolism. In 647 patients dicumarol was administered within forty-eight hours after the operative procedure, and in this group the percentage of thrombosis was reduced by 80 per cent as compared to the control series.

The author concludes that superficial femoral vein interruption when properly carried out is a safe procedure, but it does not entirely eliminate subsequent infarction, and, furthermore, it fails to protect a few patients from fatal embolism. Early treatment of thrombophlebitis by either anticoagulants, repeated paravertebral sympathetic blocks, or superficial femoral vein interruption hastens the recovery from the disease and reduces disabling sequelae.

ABRAMSON

DeBakey, M., and Ochsner, A.: Phlegmasia Cerulea Dolens and Gangrene Associated with Thrombophlebitis. Surgery **26**: 16 (July), 1949.

Vasospasm associated with deep thrombophlebitis may be severe enough to simulate arterial occlusion; in some instances it may even produce gangrene. In one type known as pseudoembolic phlebitis, the onset of the deep thrombophlebitis is with sudden excruciating pain, first located in the calf or groin, but eventually involving the whole limb. At the same time discoloration of the limb appears, taking the form of a deeply violaceous or cyanotic hue, with purpuric areas or petechial-like lesions scattered over the extremity. Swelling is generally quite marked, and associated with its onset, cutaneous blebs and even bullae may appear. At the same time pulsations in the arteries of the extremities become diminished and may even disappear, and there is a reduction in cutaneous temperature of the limb. Clinical manifestations of circulatory collapse often accompany or immediately follow the onset of the condition, and death may occur subsequently. In another type, actual gangrene of a part of the extremity may follow the deep thrombophlebitis; or the sequence of events may be reversed, with the arterial manifestations appearing first and signs of involvement of the venous system later. The prognosis in these cases is not good, death having occurred in approximately half the reported cases.

Therapy under such conditions is generally not too successful. Vasodilating procedures, such as the use of acetylcholine, Papaverine, or paravertebral sympathetic blocks, are generally of only temporary benefit. Nor has operative intervention in the form of exposure of the femoral vessels, thrombectomy and periarterial sympathectomy been found to be very efficacious. A conservative attitude should be taken toward amputation, which should be postponed until the full extent of the eventual loss of tissue has become apparent.

Two factors, arterial spasm and massive venous obstruction, have been postulated as responsible for the striking arterial manifestations in the severe types of venous thrombosis. To the authors, the second possibility appears to be more plausible. Obstruction of the venous return in an extremity, provided that it is of sufficient extent, can cause a great reduction in the arterial blood flow. However, in addition to being practically complete, the blockage must take place suddenly in order to produce enough anoxia of tissue to result in gangrene. This may conceivably initiate an immediate and severe degree of vasospasm which further tends to aggravate the ischemic process. Fortunately, because of the richness and abundance of the collateral venous channels generally present, gangrene is only very infrequently a part of the clinical picture of deep thrombophlebitis.

ABRAMSON

Goodman, L.: Recurrent Hypertensive Cerebral Thrombosis. Arch. Neurol. & Psychiat. **62**: 445 (Oct.), 1949.

The author studied 6 cases of recurrent cerebral thrombosis in hypertensive patients. The average

age at onset was 40 years. The average age at death was 52.6 years. The average span of life was 11.4 years after the onset of hypertensive symptoms. The average systolic blood pressure was 223 mm. of mercury. The average diastolic pressure was 123 mm. of mercury. Neurologic or mental symptoms or both were the initial manifestations in all cases. The vascular disease primarily affected the arteriolar system; involvement was maximal in the brain. In only 2 cases was the arteriolar disease in the renal parenchyma as diffuse and as severe as in the brain. In 3 cases, arteriolar disease in the kidneys was far advanced, but either less diffuse or associated with less microscopic parenchymal change than in the brain. The arterioles of the heart were but moderately sclerotic in 4 cases and practically devoid of arteriosclerotic changes in 2 cases. The coronary arteries and their terminal branches were spared to a surprising degree. The factors common to all the cases reported were hypertension, vasospasm, arteriolar sclerosis (cerebral and renal chiefly) and cerebral ischemia and edema.

BELLET

Clifton, E. E., and Neel, J. C.: Ligation of the Vena Cava in Extending Thrombophlebitis. Arch. Surg. **59**: 1122 (Nov.), 1949.

On the basis of a study of 2 cases, the authors present a clinical syndrome which they believe indicates the existence of an ascending thrombophlebitis in the inferior vena cava. The manifestations include pain and tenderness in the lumbar region and the loin and hyperesthesia in the distribution of the lumbar nerve; these are due to involvement of the lumbar veins or the collateral veins by the spread of the thrombophlebitis. According to the authors, ligation of the inferior vena cava is indicated in the treatment of this condition.

ABRAMSON

Spitzer, J. M., Rosenthal, N. Weiner, M., and Shapiro, S.: Pulmonary Embolism: Its Incidence at Necropsy in Relation to Peripheral Thrombosis. Ann. Int. Med. **31**: 884 (Nov.), 1949.

Peripheral venous thrombosis and pulmonary embolism are not parallel phenomena. In 202 consecutive patients who died of miscellaneous causes, excluding liver disease, the incidence at necropsy of cardiac or venous thrombosis was 33 per cent, whereas pulmonary embolism occurred in 14 per cent of the total number. The latter complication predominated in the older age group. On the other hand, in 97 cases of fatal portal cirrhosis, no pulmonary emboli were found, even though the incidence of cardiac and peripheral venous thrombosis in these 97 cases of liver disease was not significantly different from that of the miscellaneous group. Hypocoagulability of the blood cannot explain this difference since decreased coagulability is just as often observed in aged patients as in patients with cirrhosis of the liver. Therefore, factors other than changes in coagulability of the blood must be sought to explain the occurrence of pulmonary embolism.

WENDKOS

Zak, F. G., and Elias, K.: Embolization with Material from Atheromata. Am. J. M. Sc. **218**: 510 (Nov.), 1949.

Three cases of embolization with material from atheromata are reported. The first of these represented the chronic or healed phase of such embolization, the origin being eroded atheromata of the aorta. The second represented an instance of embolization by material from an atheroma in the right coronary artery associated with myocardial scars. In the third case there was embolization with material from an unusually large arteriosclerotic valve ring. To the authors' knowledge, no similar case has been reported.

The authors believe that embolization with atheromatous material is more common than generally assumed. The pathologist usually sees the late or healed form. The acute phase of the process may represent itself as a panarteritis with many eosinophils, necessitating serial sections for the elucidation of its true nature. Foreign body giant cell formation and intimal thickening are later phases of this process. Scars, for example, in the kidneys, may be caused by these emboli and microscopic scarring of the myocardium may have a similar origin.

DURANT

Mason, E. C., and Harrisin, S. P.: The Production and Prevention of Thrombosis and Embolism. Surg., Gynec. & Obst. **89**: 640 (Nov.), 1949.

A study was undertaken to analyze and illustrate the mechanism of production and the prevention of thrombosis and embolism. For this purpose a simple artificial circulatory system was set up and filled with freshly heparinized blood. The side arm was packed with a wick through which controlled amounts of tissue extract could be added. It was found that thrombus formation was initiated at the base of the side arm where the circulating blood came in contact with the tissue extract, the growth of the thrombus being in the direction of blood flow. The production of the clot depended upon the rate of blood flow and the rate at which tissue extract was introduced. When the circulation was rapid, even large amounts of tissue extract were ineffective in producing a thrombus. On the other hand, with a slow blood flow, the introduction of a small amount of tissue extract was sufficient to cause clotting. It was pointed out that heparin owes its value in the prevention of intravascular clotting to its power to neutralize thromboplastin.

ABRAMSON

Moolten, S. E., Vroman, L., Vroman, G. M. S., Goodman, B.: Role of Blood Platelets in Thromboembolism. Arch. Int. Med. **84**: 667 (Nov.), 1949.

The massing of blood platelets as an adherent plug is the primary event in thrombosis. The platelet plug (white thrombus) is the principal means of attachment of the blood clot (red thrombus) until the latter is organized by invading fibroblasts. Clot retraction before organization favors the detachment of emboli. Endothelial "wettability" and platelet adhesiveness are the principal governing factors in thrombosis. Experiments are described demonstrating relative nonwettability in unopened blood vessels and the progressive development of wettability under conditions which probably favor thrombosis.

An increase in the number and adhesiveness of platelets results from the action of thrombocytosin, a lipid of body fat, which is probably liberated by direct trauma, by proteolytic or lipolytic ferments activated by tissue breakdown of any type or after the ingestion of dietary fat of animal origin. Thrombocytopen, a lipid of the spleen which suppresses platelet formation and adhesiveness, is probably the physiologic antagonist of thrombocytosin. Thus, its use is suggested in the prophylaxis of thrombosis. Thrombocytosin has been found useful in the therapy of purpura.

A new method of measuring platelet adhesiveness to wet-table surfaces is described in which citrated blood is filtered through a wick of glass wool. By this test, platelet adhesiveness is found particularly high and persistent in cancer. Similar findings occur in polycythemia vera, idiopathic thrombocythemia and related conditions, which probably represent primary disorders of the bone marrow rather than a response to thrombocytosin. Heparin sodium tends to lower platelet adhesiveness and probably retards lysis. Dicumarol has much less effect.

The observations suggest that deficient splenic function may be one of the factors which predispose to thrombosis. Conversely, normal splenic function may include protection of the circulatory tree against thrombosis.

BERNSTEIN

Roe, B. B. and Goldthwait, J. C.: Pulmonary Embolism. New England J. Med. **241**: 679 (Nov. 3), 1949.

The authors attempted a statistical analysis of patients who died of pulmonary embolism and in whom vein ligation had been performed. They concluded that a five-year, large scale program of femoral vein interruption had failed to alter the mortality figures for pulmonary embolism, as compared with earlier, similar periods during which this procedure was not carried out. However, because of the many conditions which defied statistical analysis, no final conclusion could be reached regarding the value of the program.

ABRAMSON

VASCULAR DISEASE

Intermittent Venous Occlusion. Lancet **2**: 157, (July 23) 1949.

This editorial points out that no physiologic evidence has appeared to indicate that the clinical procedure of intermittently applying venous occlusion pressures to a limb produces an immediate vasodilating effect upon the vessels locally. However, since clinical studies indicate that some beneficial effects follow its long continued use, and since no harm ensues from such a program except in the presence of moist gangrene, the method appears to be worthy of further trial.

ABRAMSON

Linton, R. R.: The Arteriosclerotic Popliteal Aneurysm. Surgery **26**: 41 (July), 1949.

Spontaneous aneurysm is present more frequently in the popliteal artery than in any other vessel of the body except the thoracic aorta. Although syphilis plays an important role in the etiology of aneurysms, the author was able to show in his series that arteriosclerosis as well is responsible for this type of lesion, particularly in the case of patients falling into the older age groups. His report deals with the surgical treatment of 14 cases of the arteriosclerotic type of popliteal aneurysm.

In 11 of the patients, the aneurysm developed spontaneously, while in the remaining 3 it followed trauma. In most instances pain in the popliteal space was the predominant symptom; arterial pulsations were detectable in all the aneurysms.

In all cases a preliminary sympathectomy was performed, and followed by an aneurysmectomy seven to eleven days later. In no instance did gangrene of the extremity occur after removal of the aneurysm. One patient in the series died after sympathectomy. Both procedures were not done at the same time because of the danger of surgical shock, with the possibility of a drop in arterial pressure producing irreversible vascular changes in the involved limb and gangrene.

The author concludes that a patient presenting an arteriosclerotic popliteal aneurysm, irrespective of age, should be considered a candidate for its surgical removal, unless his cardiac condition contraindicates such treatment, or unless the aneurysm has become thrombosed spontaneously and produced gangrene of the extremity. Preliminary sympathectomy appears to be of value in maintaining the circulation of the limb.

ABRAMSON

Coller, F. A., Campbell, K. N., Harris, B. M., and Berry, R. E. L.: The Early Results of Sympathectomy in Far-Advanced Arteriosclerotic Peripheral Vascular Disease. Surgery **26**: 30 (July), 1949.

The authors attempted to evaluate the therapeu-

tic effects of sympathectomy in far-advanced arteriosclerotic peripheral vascular disease on the basis of a study of 63 patients in whom this operation had been performed on one or both lower extremities. Twenty-one individuals in the series also had diabetes mellitus.

About half the patients who experienced rest pain were relieved of this symptom; others showed some alleviation of the pain. Of the 13 patients who were not helped, 11 subsequently had to have amputations. Most of the patients complaining of cold feet were helped by the operation. Some benefit was experienced with regard to intermittent claudication in 27 of 31 cases, but no patient obtained unlimited walking distance. Ulceration of the skin healed rapidly after sympathectomy in approximately half the cases. The remainder received little if any benefit from the operation. Gangrene was arrested in 28 of 40 patients, while in 11, amputation still had to be performed. There was one death in the series.

Since the maximum benefits of operation frequently were observed as long as one year after operation, the authors were of the opinion that the elimination of vasospasm by the procedure could not alone account for the beneficial effects and that the possibility of a hypertrophy of the collateral arterial network had also to be considered. However, it must be pointed out that 19 patients stopped smoking after operation and that in 18 of these good results were obtained, thus suggesting that abstinence from smoking might also have played a role.

Among the untoward effects from the operation were rapid onset of gangrene in 2 cases, postoperative neuralgia which lasted for less than two weeks, and in 5 patients, a delayed swelling of the sympathectomized limb.

ABRAMSON

Hermann, L. G., and Buchman, J. A.: Complications Resulting from Injuries to Major Arteries. Surgery **26**: 59 (July), 1949.

There are a number of different complications which may follow injury to major arteries and their concomitant veins, the most common being spasm of the involved vessel or of the entire arterial bed. This may last for hours or even days, and as a result of the associated arterial insufficiency, serious and irreversible changes may occur in the skin, nerves, muscles and joints of the limb. Repeated paravertebral sympathetic blocks may overcome the peripheral vasoconstriction. Another complication of injury to arteries is hemorrhage. This must be controlled immediately not only because of the loss of blood which takes place but also because an ample supply of blood to the parts beyond the point of injury must be maintained or serious changes are certain to follow. When a major artery is merely contused and the coats of the vessel are not ruptured, the damage to the intima may be sufficient to cause local intravascular clotting of the blood and subsequently extension into, and thrombosis of, the collateral arterial circulation. Arterial and arteriovenous aneurysms may also follow damage to a major vessel.

ABRAMSON

Handler, J. J.: Acute Arterial Spasm Complicating Accidental Haemorrhage in Late Pregnancy. Lancet **2**: 514 (Sept. 17), 1949.

The author presents a case report of a female patient who developed marked spasm of both the internal and external iliac arteries on one side, associated with severe vaginal bleeding, late in pregnancy. A sympathectomy was followed by a slow return of pulsations and reappearance of normal function in the extremity. The shock state, together with the pressure of a distended uterus against the vessels, was considered to be responsible for the arterial spasm in the limb.

ABRAMSON

Pemberton, H. S., and Watson, D. C.: Ontophoresis in Treatment of Peripheral Vascular Disease. Brit. M. J. **4628**: 633 (Sept. 17), 1949.

The author investigated the effect of Mecholyl by iontophoresis on a series of 83 patients suffering from arteriosclerosis obliterans, Raynaud's disease, thrombophlebitis or acrocyanosis. Satisfactory or partial improvement was noted in 56 cases, the best results being obtained in the cases of arteriosclerosis obliterans with intermittent claudication and in those with diabetic gangrene. In the patients with Raynaud's disease, Buerger's disease and acrocyanosis, the therapeutic effect was disappointing.

ABRAMSON

Graveson, G. S.: Retinal Arterial Occlusion in Migraine. Brit. M. J. **4632**: 838 (Oct. 15), 1949.

The occurrence of severe retinal arterial spasm in the early phase of attacks of migraine may lead to a permanent defect in vision. This type of rare complication was noted by the author in four cases, in each of which retinal arterial occlusion occurred during an attack.

On the basis of such findings and others in the literature, the author expresses the opinion that the symptoms of migraine result from alteration in the calibre of blood vessels in the head and that both intracranial and extracranial vessels take part in the process. During an attack two stages are recognized: (1) the stage of preheadache symptoms, consisting of visual disturbances, paresthesias and aphasia, and considered to be due to functional disturbances of cortical cells secondary to the anoxemia produced by intracranial angiospasm; and (2) the stage of headache produced by an excessive dilatation, particularly of extracranial arteries, which stimulates the pain nerve endings accompanying these vessels.

ABRAMSON

Derr, J. W., and Noer, R. J.: Experimental Mesenteric Vascular Occlusion. Surg., Gynec. & Obst. **89**: 393 (Oct.), 1949.

The present studies were undertaken to determine the survival potential of a constant length of small intestine subjected to arterial, venous or combined vascular occlusion in various levels of the small gut. The authors conclude that (1) in experimental vascular occlusion, ligation in continuity is not a dependable method; division is necessary to insure interruption of a given vessel. (2) Interruption of any or all of the mesenteric supply to a 15 cm. segment of the dog's small intestine results in death of less than half of the animals treated. (3) In the dog complete vascular deprivation of a segment 15 cm. or less in length cannot be accomplished uniformly by interruption of intestinal and arcuate vessels. (4) Contrary to the usual assumption, in this series, venous ligation produced no higher mortality than ligation of any other vessel or combination of vessels. (5) In the dog there appears to be no significant difference between the revascularization potential of different levels of the small intestine. (6) The great revascularizing ability of the canine intestine is strikingly demonstrated by these experiments. The role played by the intramural vessels and their anastomotic connections needs further investigation as does the effect of associated distention of the gut.

BECK

Goldstein, P.: Spontaneous Rupture of Syphilitic Saccular Aneurysms of the Ascending Aorta into the Pericardial Cavity, with Hemopericardium. Arch. Int. Med. **84**: 540 (Oct.), 1949.

The author presents 29 cases of sudden and unexpected natural death in which the cause of death was spontaneous rupture of a syphilitic aneurysm of the ascending aorta into the pericardial cavity with resultant hemopericardium and cardiac tamponade. The ages of the patients ranged from 17 years to 78 years. Twenty-three men and 6 women, 11 of whom were white persons and 17 of whom were Negroes, were included in the series.

Twenty-seven deaths were due to rupture of the ascending aorta in that part which lies within the pericardial reflection. In 2 cases, death was due to aneurysms which were outside the pericardial reflection but which had eroded into the pericardial cavity. Anatomically, syphilitic aneurysm of the ascending aorta may rupture into the right atrium, the right ventricle, the conus arteriosus, the pulmonary artery, the superior vena cava, the left atrium, the right bronchus, or, as in this series, directly into the pericardial cavity. With rupture into the pericardial sac death is usually sudden, occurring a few minutes after the rupture.

BERNSTEIN

AMERICAN HEART ASSOCIATION, INC.

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ANNUAL DINNER

The Annual Dinner of the Association will be held in the Gold Room, Fairmont Hotel, San Francisco, on Saturday, June 24, 1950 at 7:30 P.M. Members are invited to bring their family and friends. Reservations, at a cost of $7.00 each, should be sent to the Association as soon as possible.

WASHINGTON CONFERENCE ABSTRACT AVAILABLE

An abstract of the proceedings of the National Conference on Diseases of the Heart and Circulation, held in Washington last January 18–20, is now available. A complete edition of all the reports and papers also will be ready shortly. Copies of both of these publications may be obtained by writing to Dr. John W. Ferree, Public Health Director of the Association.

INTERNATIONAL CARDIOLOGICAL CONGRESS IN PARIS

A meeting of the International Cardiological Congress will be held in Paris September 3–9, 1950. All papers read at the meeting will be published in the Archives des maladies du coeur.

Publishers of medical books have been invited to exhibit books on cardiology published

since 1930, as well as sample numbers of periodicals in this field. Only material directly pertaining to cardiovascular diseases will be shown. Shipments should be sent by mail to reach the following address before June 1, 1950:

Exposition du Congrès International
de Cardiologie
Faculté de Médecine
12, Rue de l'Ecole de Médecine, Paris
(VI)

At the same the books are sent, the publishers should send a list indicating the exact sale price of these volumes to the following address:

Librairie Baillière
19, Rue Hautefeuille, Paris (VI)
Attention: International Cardiological
Congress.

A commercial service will be established near the exhibition, and a record will be made of all orders requested by the visitors. These orders will be transmitted to each foreign publisher.

After the Congress, all books which have been exhibited will be sent as a gift to the Library of the Faculty of Medicine in Paris, in appreciation of its organization of the Congress. This arrangement will avoid customs duties, the expense of reshipment and payments, which are difficult to arrange with certain countries. Material will be accepted for exhibition only under these conditions.

INTERNATIONAL SOCIETY FOR INTERNAL MEDICINE

The International Society for Internal Medicine will hold its first formal meeting in Paris immediately following the Cardiological Congress. The program is being prepared under the direction of Professors A. Gigon of Basle and Nanna Svartz of Stockholm.

Professor Gigon may be reached at 1 Hebelstrasse, Basle, Switzerland, and Professor Svartz at Karolinski Sjukhuset, Stockholm 60, Sweden.

Further information about the meetings may be obtained from Doctor Albert M. Snell, Palo Alto Clinic, 300 Homer Avenue, Palo Alto, California.

NEW AFFILIATES OF HEART ASSOCIATION

Affiliation of the following heart associations has been approved by the Board of Directors: New Mexico Heart Association, Virginia Heart Association, Great Falls Area (Montana) Heart Association, Westchester (County, N. Y. State) Heart Association, and Arkansas Heart Association, Inc. This brings to 61 the total of state and local heart associations now affiliated with the national Association.

COUNCIL FOR RESEARCH ON HIGH BLOOD PRESSURE

The Council for High Blood Pressure Research has elected the following as members of its Medical Advisory Board: Dr. Wright Adams, Chicago; Dr. Benjamin N. Baker, Jr., Baltimore; Dr. M. A. Blankenhorn, Cincinnati; Dr. William H. Bunn, Youngstown, O.; Dr. George E. Burch, New Orleans; Dr. Arthur C. Corcoran, Cleveland; Dr. George K. Fenn, Chicago; Dr. William J. Kerr, San Francisco; Dr. William Kountz, St. Louis; Dr. Arthur Merrill, Atlanta; Dr. George A. Perera, New York; Dr. William P. Thompson, Los Angeles; Dr. Francis C. Wood, Philadelphia; Dr. Irving S. Wright, New York.

Officers of the Medical Advisory Board are Dr. Robert W. Wilkins, Boston, Chairman; and Dr. Edgar V. Allen, Rochester, Minn., Vice Chairman.

Newly elected Officers of the Council include: Alva Bradley, President; W. H. Gerhauser, Vice President; Adrian D. Joyce, Vice President; George E. Merrifield, Secretary; I. F. Freidenberger, Treasurer. All reside in Cleveland.

The Nominating Committee of the Medical Advisory Board includes Dr. Thomas Findley, New Orleans, Chairman; Dr. Meyer Friedman, San Francisco; Dr. Keith S. Grimson, Durham, N. C.; Dr. Francis D. Murphy, Milwaukee; Dr. George E. Wakerlin, Chicago.